Prescribing patterns of antibiotics in Lesotho public health institutions

M.K.B. Adorka

Prescribing patterns of antibiotics in Lesotho public health institutions

M.K.B. Adorka

Thesis submitted for the degree Doctor of Philosophy in Pharmacy Practice at the Potchefstroom Campus of the North-West University.

Promoter:	Prof J.H.P. Serfontein
Co-Promoter:	Prof M.S. Lubbe
Co-Promoter:	Prof A.G.S. Gous

May, 2010

Dedication

I dedicate this work to:

- My elder brother, **Johnson Kwadzo Agbeti-Adorka** for granting me the opportunity to education, an opportunity he denied himself for my sake

- To past presidents **Dr Kwame Nkrumah** and **Jerry John Rawlings** of my country Ghana, whose honesty and hard work, dedication to the course of justice, and exemplary leadership styles, have had a significant impact on my philosophy of life

Acknowledgements

God Almighty takes the glory for the initiation and completion of this work. He is indeed a faithful God whose promises never fail.

My foremost gratitude for this work goes to the following persons at the North-West University for their various contributions in the conduct of this research and support of my efforts in compiling this thesis.

- My promoters, Professors J.H.P. Serfontein, M. S. Lubbe for their academic guidance.
- Prof H.S. Steyn of the Statistics Consultation Services and here again to Prof Lubbe for the significant role they played in the analysis of the research data.
- The entire staff of the Pharmacy Practice Department for their moral support. I mention here particularly Ms A. Bekker and Mr W.D Basson, for their technical assistance.
- Ms M.M. Terblanche for proof reading and upgrading the grammatical use of the language for this 800 page thesis.

Sources of financing the collection and electronic capture of data for this research came from the National University of Lesotho and the Niche Area Medicine Usage of South Africa. I express my sincere gratitude to these institutions.

My appreciation and thanks also go to the following at the National University of Lesotho.

- To former Vice and Pro-vice Chancellors, Professors M. M. Sejanamane and T. M. Makatjane for their personal support as I got on this project.
- To Mr S. Amaka of the English Language Department of the Faculty of Humanities for his assistance in editing portions of the thesis
- To Mr M. Ntlama, the manager of the Stationery and Printing department, the Bursar Mr J.J. Sekoere and Mr Mugomeri of the Faculty of Health Sciences, for the various ways in which they assisted me in printing and binding copies of this thesis.
- To Prof P. O. Odonkor, Dean of the Faculty of Health Sciences, for his support, encouragement and guidance as I pursued this programme
- To Dr T. Makoa and the entire staff of the Faculty of Health Sciences for their support and encouragement.
- To all students of the Bachelor of Pharmacy Honours degree programme of the National University of Lesotho who willingly assisted me in the field collection, summarization and

electronic capture of the research data for this work. I particularly mention in this regard Ms T.M. Lebeko, Ms M.S. Lerata, Ms T.C. Ralimpe, and Ms N. Moketsepane for their support and the diverse ways in which they assisted me in organising the research data for analysis.

The Ministry of Health & Social Welfare lent me a major support as I undertook this project. I extend in this regard my profound gratitude to the following:

- To the former Director General of Health Services (DGHS) of the Ministry, Dr H. M. Morosi, for granting me the permission and encouraging me to conduct this research. The importance he attached to this work and its potential benefit to the health delivery system of Lesotho greatly motivated me to carry it out this study to its logical conclusion.
- To J. Nkonyana, Head of the Epidemiological Unit of this Ministry for helping me develop questionnaires for Phase III of this research.
- To the Medical Superintendent of the Queen Elizabeth II and the District Medical Officers (DMOs) of the Motebang, Berea, Maluti and Scott Hospitals for granting me the permission to conduct this research in their hospitals.
- The Pharmacy and Medical Laboratory staffs of the study site hospitals for the assistance and cooperation they gave me in collecting data for this study.

I further express my utmost gratitude to the following relatives of mine.

- To my loving wife, Lineo Mpela-Adorka for her unflinching support.
- To my wonderful children, Neko, Anyo, Esenam, Seyram and Selorm. The validation of who I am as a father to them and an icon of a human they look up to and emulate in life, placed a value on me. This value gave me the self esteem and motivation I needed for this work.
- To Dr John Wayem of the UNDP, Dr C. K & Dr (Mrs) Hoedoafia, Mssrs Henry Akutsa and Justice Y. Adzimah, for joining hands in removing emotional stresses and financial hiccups that severally threatened my focus as I pursued this programme.
- To Bishop James Dinu, in his capacity as a mathematician and educator in mathematics, for validating mathematical concepts I used in developing formulae for quantifying the characteristics of antibiotics that are considered in principle in the selection of these agents in the empiric treatment of infections.

SUMMARY

KEY WORDS: Principles, antibiotic prescribing, influencing factors, antibiotic prescriptions, appropriateness, bacterial pathogens, antibiotic sensitivity patterns, antibiotic selection, empiric treatment of infections.

In Lesotho, a relatively poor country, empiric use of antibiotics, rather unsupported by sufficient knowledge of the sensitivities of bacterial pathogens to the agents, is by observation a mainstay of treating infections. Such manners of antibiotic prescribing were witnessed as would not altogether be conducive to appropriate prescribing, contrary to an urge of the World Health Organisation for countries to use antibiotics appropriately as a strategy for curbing bacterial pathogen antibiotic resistance development. The purpose of this study, was to investigate, *inter alia*, the extent to which antibiotics are appropriately prescribed and to make available baseline information that would assist in the formulation of relevant policies on the judicious use of the drugs.

Conducted in three phases and in accordance with its set objective, the study generally investigated the extent to which antibiotics were appropriately prescribed and the impact of antibiotic prescribing on treatment outcomes and related costs identified bacterial pathogens commonly associated with diagnosed infections, made predictions of the clinical effectiveness of antibiotic prescribing for diagnosed infections, identified factors that principally would influence prescribers' manner of prescribing antibiotics and developed procedures to enhance the appropriate selection of antibiotics in the empiric treatment of infections.

A novel method based on prescribers' adherence to principles of antibiotic prescribing was developed and used in assessing the appropriateness of antibiotic prescriptions. Data on antibiotic prescriptions were collected prospectively from inpatient and outpatient departments of selected hospitals. Data on bacterial pathogen sensitivities to formulary antibiotics, similarly, were collected retrospectively from records of culture sensitivity test results as kept by microbiology laboratories of study site hospitals. Analysis of data was done to show associations of pathogens with diagnosed infections and their sensitivity patterns to formulary antibiotics. A formula for quantifying the activity and cost characteristics of antibiotics was developed and used in selecting antibiotics most appropriate in the empiric treatment of given infections. A structured questionnaire survey that targeted prescribers at health service areas of

study site hospitals and aimed at investigating factors that influence prescribers' manner of antibiotic prescribing was also carried out.

Results of the study showed that antibiotics were most often prescribed inappropriately in inpatient departments, as compared to outpatient departments. Appropriate antibiotic prescribing in inpatient departments appear to have a positive impact on treatment outcomes and costs of antibiotic treatment. Ampicillin and metronidazole and ampicillin and co-trimoxazole were observed as the first and second most frequently prescribed antibacterial agents in inpatient and outpatient departments respectively. Pathogens predominantly associated with given infections in inpatient departments of study site hospitals were identified as *Staphylococcus aureus* for lower respiratory tract, eye, ear, and skin and soft tissue infections; *Streptococcus pneumoniae* for meningitis; *Escherichia coli* for ascites and urinary tract infections; and *Proteus* spp for septicaemia. Between January 2000 and December 2005, substantial increases in resistance to cloxacillin, ampicillin, co-trimoxazole and cefotaxime were noticed for *Staphylococcus aureus.* Similar increases in the case of co-trimoxazole were observed for *E. coli* and *Klebsiella* spp. Among gram-positive cocci, ampicillin demonstrated the highest activities against *S. pneumoniae* and *S. pyogenes*. Activity of gentamicin against gram-negative bacilli was largely preserved despite the high rate of prescribing the antibiotic in inpatient departments. A large majority of prescribers prescribe antibiotics commonly whenever they are not sure of the aetiologies of diagnosed cases. A majority of prescribers composed of all qualification categories also lack adequate knowledge in bacteriology and principles of antibiotic prescribing. Shortcomings exist in mechanisms of disseminating results of tests on microbial examination of specimens to prescribers.

In line with findings of this study, it is recommended that the Ministry of Health and Social Welfare institute measures aimed at improving antibiotic prescribing in the country's health institutions. It is particularly recommended that policies be formulated with regard to appropriate prescribing of antibiotics; development of user friendly algorithms of infection diagnosis and treatment; improvement of functional capabilities of microbiology laboratories *vis a vis* the institution of effective information network systems for information dissemination on patterns of microbial resistance to commonly used antibacterial agents; and also the education of prescribers on antibiotic prescribing.

OPSOMMING

SLEUTELWOORDE: Beginsels, voorskryf van antibiotika, beïnvloedende faktore, antibiotikavoorskrifte, geskiktheid, bakteriële patogene, sensitiwiteitspatrone van plaaslike antibiotika, keuse van 'n antibiotikum, empiriese behandeling van infeksies

In Lesotho, 'n relatief arm land, is die empiriese gebruik van antibiotika wat meesal nie deur voldoende kennis van die sensitiwiteit van bakteriële patogene vir die middels ondersteun word nie, na waarneming die steunpilaar vir behandeling van infeksies. Dit is waargeneem dat sodanige gebruik van antibiotika nie die korrekte voorskryf daarvan bevorder nie, in teenstelling met die oproep van die Wêreldgesondheidsorganisasie dat lande antibiotika oordeelkundig moet gebruik as 'n strategie om die ontwikkeling van weerstand van bakteriële patogene teen antibiotika te beperk. Die doel van hierdie studie was onder meer om die mate waartoe antibiotika toepaslik voorgeskryf word, te ondersoek en om basislyninligting beskikbaar te stel wat sal help om relevante beleid vir die oordeelkundige gebruik van hierdie medisyne te formuleer.

Die studie is volgens die gestelde doel in drie fases gedoen, waarin die mate waartoe antibiotika toepaslik voorgeskryf is en die impak wat die voorskryf van antibiotika op die uitkomste van behandeling en verwante koste het, ondersoek is, waarin bakteriële patogene wat algemeen in gediagnoseerde infeksies voorkom, geïdentifiseer is, waarin voorspellings van die kliniese effektiwiteit van die voorskryf van antibiotika vir gediagnoseerde infeksies gemaak is, waarin faktore geïdentifiseer is wat die voorskrywer se manier vir die voorskryf van antibiotika beïnvloed en waarin prosedures om die seleksie van geskikte antibiotika vir die empiriese behandeling van infeksies ontwikkel is.

'n Nuwe metode, gebaseer op die nakoming van die beginsels vir die voorskryf van antibiotika deur die voorskrywer, is ontwikkel en gebruik om die geskiktheid van voorskrifte vir antibiotika te beoordeel. Data van voorskrifte vir antibiotika is van binne- en buitepasiëntafdelings van geselekteerde hospitale versamel. Data van die sensitiwiteit van bakteriële patogene vir antibiotika is soortgelyk retrospektief van die rekords van sensitiwiteitstoetse van die mikrobiologiese laboratoriums van die hospitale van die studie verkry. 'n Ontleding van die data is gedoen om die verband tussen patogene en gediagnoseerde infeksies en hulle sensitiwiteit teenoor antibiotika te toon. 'n Formule om die aktiwiteit en die koste van antibiotika te

kwantifiseer, is ontwikkel en gebruik om die mees geskikte antibiotika vir die empiriese behandeling van gegewe infeksies te kies. 'n Ondersoek met 'n gestruktureerde vraelys wat voorskrywers in areas van gesondheidsorg by die studiehospitale geteiken het en daarop gemik was om die faktore wat voorskrywers se manier vir die voorskryf van antibiotika te bepaal, is ook gedoen.

Resultate van die studie het getoon dat antibiotika meer dikwels in binnepasiëntafdelings as in buitepasiëntafdelings ontoepaslik voorgeskryf word. Dit lyk asof die toepaslike voorskryf van antibiotika in binnepasiëntafdelings 'n positiewe invloed op die uitkomste en die koste van behandeling met antibiotika het. Dit is opgemerk dat ampisillien en metronidasool, en ampisillien en kotrimoksasool die antibakteriële middels is wat die meeste en tweede meeste in die binne- en buitepasiëntafdelings onderskeidelik voorgeskryf word. Patogene wat hoofsaaklik met gegewe infeksies in die binnepasiëntafdelings van die studiehospitale gepaardgaan, is as *Staphylococcus aureus* vir infeksies van die onderste lugweg, oë, ore, vel en sagte weefsel, *Streptococcus pneumoniae* vir meningitis, *Escherichia coli* vir askites en urienweginfeksies en *Proteus* spp vir septisemie geïdentifiseer. Tussen Januarie 2000 en Desember 2005 is beduidende toename in die weerstand van *Staphylococcus aureus* teen kloksasillien, ampisillien, kotrimoksasool en kefotaksiem waargeneem. Soortgelyke toenames is in die geval van *E. coli* en *Klebsiella* spp. teen kotrimoksasool waargeneem. Van die gram-positiewe kokke het ampisillien die sterkste aktiwiteit teen *S. pneumoniae* en *S. pyogenes* getoon. Aktiwiteit van gentamisien teen gram-positiewe basille is grootliks behou ten spyte van die groot mate waartoe dié antibiotikum in binnepasiëntafdelings voorgeskryf is. Die oorgrote meerderheid voorskrywers skryf antibiotika algemeen voor selfs al is hulle nie seker van die etiologie van gediagnoseerde gevalle nie. 'n Groot deel van voorskrywers van alle kategorieë wat kwalifikasies betref, het nie voldoende kennis van bakteriologie en die beginsels vir die voorskryf van antibiotika nie. Daar is tekortkominge in die meganismes vir die verspreiding van toetsuitslae van mikrobiologiese ondersoeke van monsters aan voorskrywers.

Ooreenkomstig die bevindinge van hierdie studie word aanbeveel dat die minister van gesondheid en maatskaplike welsyn maatreëls instel wat daarop gemik is om die voorskryf van antibiotika in die land se gesondheidsinrigtings te verbeter. Dit word veral aanbeveel dat beleid geformuleer word vir die toepaslike voorskryf van antibiotika, die ontwikkeling van gebruikersvriendelike algoritmes vir die diagnose en behandeling van infeksies, vir die verbetering van die funksionele vermoë van mikrobiologiese laboratoriums ten opsigte van die

instel van effektiewe netwerkstelsels vir die verspreiding van inligting oor die patrone van mikrobiese weerstand teen antibakteriële middels wat algemeen gebruik word en ook vir die opvoeding van voorskrywers vir die voorskryf van antibiotika.

TABLE OF CONTENTS

CHAPTER TWO - BACTERIAL PATHOGENS, ANTIBIOTICS, PRINCIPLES OF ANTIBIOTIC PRESCRIBING 17

LIST OF TABLES

LIST OF FIGURES Page

LIST OF APPENDICES

LIST OF ABBREVIATIONS

ADP	Adenosine diphosphate
AIDS	Acquired immune deficiency syndrome
AOM	Acute otitis media
ARI	Acute respiratory infection
ATFR	Antibiotic treatment failure rate
ATP	Adenosine triphosphate
ATSFR	Antibiotic treatment success to failure ratio
ATSR	Antibiotic treatment success rate
C5a	Cytokine 5a
cAMP	Cyclic adenosine monophosphate
CHAL	Christian Health Association of Lesotho
CHAL	Christian Health Association of Lesotho
CHW	Community Health Worker
CNS	Central nervous system
CoNS	Coagulase-negative staphylococci
CSF	cerebrospinal fluid
CSF	Cerebrospinal fluid
CST	Culture sensitivity test
CST	Culture sensitivity test
DAEC	Diffusely adherent E. coli
DCT	Data collection tools
EAEC	Entetroaggregative E. coli
EHEC	Enterohaemorrhagic E. coli
EIEC	Enteroinvasive E. coli
EML	Essential medicines list
EPEC	Enteropathogenic E. coli
ETEC	Enterotoxigenic E. coli
ExPEC	Extraintestinal pathogenic E. coli
FUO	Fever of unknown origin
FWs	Field workers

FGC	Fourth generation cephalosporins
GABA	Gama aminobutyric acid
GIT	Gastrointestinal tract
GNB	Gram-negative bacilli
GUT	Genitourinary tract
GUTI	Genitourinary tract infections
HC	Health Centre
Hib	H influenzae type b
HIV	Human immunodeficiency virus
HSA	Health Service Area
HSA:	Health Service area
HUS	Haemolytic uraemic syndrome
ICARE	Intensive Care Antimicrobial Resistance Epidemiology
IL-1	Interleukin -1
IL-6	Interleukin -6
IL-8	Interleukin -8
LOS	Lipooligosaccharides
LPS	Liposaccharides
LRTI	Lower respiratory tract infection
MAI	Medication appropriateness index
MOHSW	Ministry of Health and Social welfare
MRSA	Methicillin resistant Staphylococcus aureus
MS-CNS	Methicillin susceptible coagulase-negative Staphylococcus aureus
MSSA	Methicillin susceptible Staphylococcus aureus
NAD	Nicotinamide adenine dinucleotide
NADP	Nicotinamide adenine diphosphate
NDSO	National Drug Service Organisation
NC	Nurse Clinician
NHTC	National Health training College
non-SPRPs	Non-semisynthetic penicillinase resistant penicillins
NSTUTI	Non-sexually transmitted urinary tract infections
OMP	Outer membrane protein
PAI	Prescribing appropriateness index
PCAW	Percentage cost of antibiotics wasted

PFI	Percentage frequency of isolation
PID	Pelvic inflammatory disease
PMNs	Polymorphonuclear neutrophils
POA	Percentage overall activity
POR	Percentage overall resistance
POU	Pyrexia of unknown origin
PostSurg-ATSR	Post-surgical antibiotic therapy success rate
PR:	Percentage resistance
PS:	Percentage sensitivity
PVCD	Percutaneous vascular closure device
PVE	Prosthetic valve endocarditis
Queen II	Queen Elizabeth II Hospital
RA	Research assistants
RTI	Respiratory tract infection
RTSR	Relative treatment success rate
SAS	Statistical Analysis Systems
SISS	Scottish Infections Standards and Strategies
SSI	Skin and soft tissue infections
SLE	Systemic lupus erythematosus
SPRP	Semi-synthetic penicillinase resistant penicillins
STG	Standard treatment guidelines
STEC	Shiga toxin-producing E. coli
TCR	Transmembrane conductance regulator
TGCs	Third generation cephalosporins
TLRs	Toll-like receptors
TNF-β	Tumour necrosis factor β
TNF-α	Tumour necrosis factor α
TSR	Treatment success rate
TSS	Toxic shock syndrome
TSST-1	Toxic shock syndrome toxin 1
UK	United Kingdom
USA	United States of America
UT	Urinary tract

LIST OF DEFINITIONS

Absolute or definite aetiologies or causative agents of infections

Absolute or definite aetiologies or absolute or definite causative agents or absolute bacterial infections were used interchangeably to mean cases where bacterial pathogens were deemed to have been established as aetiological agents or causes of infections or clinical conditions being treated with antibiotics.

Appropriate/inappropriate

Within the context of antibiotic prescribing as implied in this study,

- "**appropriate**" refers to a classification of antibiotic prescriptions assessed and considered to be prescribed according to principles of antibiotic prescribing;
- "**inappropriate**" refers to antibiotic prescriptions prescribed without the prescriber's adherence to antibiotic prescribing principles;

Adherence /non-adherence

- "Adherence": used interchangeably with appropriate to mean prescribers' keeping to principles and writing antibiotic prescriptions appropriately.
- "Non-adherence": used interchangeably with inappropriate to mean prescribers' failure to keep to principles of antibiotic prescribing.

Basotho:

Nationals of Lesotho

Blood infections

Disease conditions of the blood denoted by specific diagnoses, symptoms or symptom complexes as sourced from patient case notes and listed in Table 4.1.12 to indicate bacterial infections of the blood for which antibiotics were prescribed for treatment.

Bone infections

Disease conditions of the bone indicated by specific diagnoses, symptoms or symptom complexes as sourced from patient case notes and listed in Table 4.1.12 to denote either bacterial infections of the bone or potential sources of such infections and for which antibiotics were prescribed for treatment or prophylaxis.

Bukana

A patient's personal booklet of medical records as used in Lesotho

Case

A particular instance of disease as diagnosed and treated in a patient

Central nervous system infections

Disease conditions of the central nervous system specified by specific diagnoses, symptoms or symptom complexes as sourced from patient case notes and listed in Table 4.1.12 to indicate bacterial infections of structures of the central nervous system for which antibiotics were prescribed for treatment.

Condition of patient

Refers to the clinical state of patient or impression concluded after clinical assessment of patient with respect particularly to his or her response to treatment

Condition as applied to prescriptions

Refers to a given requirement defined by a set of criteria that a prescription needs to conform to, to enable its classification into a given category of prescriptions as defined in this work.

Cost of antibiotic prescription

The term refers to the cost of total unit doses of prescribed antibiotic(s) used in treating an infection within a specified time period that a patient was treated for an infection.

Cost of hospitalisation

Refers to total amount a patient is charged for non medical services rendered to him or her while on hospital admission for the treatment of an infection.

Criterion (plural: criteria)

A criterion (plural: criteria) by this work refers to a guideline or parameter conceptually but rationally formulated from guiding principles of antibiotic prescribing as documented in the literature for use in evaluating the appropriateness of antibiotic prescriptions in treating cases for which they were prescribed.

Days of hospitalization/ Days in hospital/ Days on treatment for infections

The terms were used interchangeably and in the context of this research meant number of days a patient stayed in hospital for treatment for infection.

Died

Used as a treatment outcome indicator to show that a patient died during the course of antibiotic treatment.

Effects ... on

Used this way "effects" of a specified parameter or factor "on" a second indicated parameter refers to the extent to which the specified parameter or factor influences the second indicated parameter.

Formulary antibiotics

Antibiotics listed in the Essential Drug List of Lesotho for use in treating various infections.

Gastrointestinal tract/abdominal infections:

Disease conditions of the digestive system denoted by prescriber indicated specific diagnoses, symptoms or symptom complexes as sourced from patient case notes and listed in Table 4.1.12 to indicate bacterial infections of organs of the system and for which antibiotics were prescribed.

General practitioners

Refers to qualifications of doctors providing medical care to all categories of patients regardless of their age and have conditions not requiring specialist attention

Genitourinary tract infections

Disease conditions of the genitourinary system indicated by specific diagnoses, symptoms or symptom complexes as sourced from patient case notes and listed in Table 4.1.12 to denote bacterial infections of organs and structures of the system other than prescriber indicated sexually transmitted infections, for which antibiotics were prescribed for treatment.

Improved

The term "improved" is used as treatment outcome indicator to mean a patient responded positively to antibiotic treatment and was described by notations in nursing notes as "feeling better" or "feeling well" or described by any such term indicating that the patient got better upon treatment with antibiotics. It was also used to indicate positive response to antibiotic treatment when a patient was monitored and classified as such.

Not improved

"Not improved" was used as a treatment outcome indicator to indicate a negative response to antibiotic treatment. It means a patient monitored for response to antibiotic treatment using a defined monitoring parameter responded by a non-abatement of the indicated monitoring parameter. It was also used to indicate negative response to antibiotic treatment when a patient was referred to another hospital due to non-response to treatment as indicated in the patient's chart or when relatives requested for a patient to be discharged for them following the patient's non- response to hospital treatment.

Nurse clinicians

Refers to nurses who have undergone post qualification training in primary health care in nursing institutions approved by the Lesotho Nursing Council and are registered as such by Council in the relevant part of the register of nurses. (LES, 1998: 106 -107, 112, 115, 116)

Nursing assistants

Refers to persons trained in aspects of nursing that qualifies them for the title and are listed as such by Council in the list of nursing assistants as prepared and maintained by the Lesotho Nursing Council (LES, 1998: 106,107,112,115,116)

Possible or suspected aetiologies or causative agents of infections

Possible or suspected aetiologies or possible or suspected causative agents of infections were used interchangeably to mean cases where bacterial pathogens have not been established without doubt as aetiological causes of infections or clinical conditions being treated with antibiotics.

Physician Specialists

The term refers to doctors who provide medical care to categories of patients with clinical conditions in areas of their specialist training.

Possible bacterial infections

Infections for which bacterial pathogens have not been positively established as aetiological agents but for which prescribers prescribe antibiotics.

Practice location

Practice location refers to the type of community, whether rural or urban, within which respondents' places of work or practices are located.

Practice type

Practice type refers to ownership of health institutions within which respondents practice.

Prescriber

The term within the context of this study applies to health professionals entrusted with the responsibility of and were seen by results of this study to be involved in prescribing antibiotics in the treatment of infections at study sites.

Rate

Used with regard to antibiotic prescribing in given infections, rate denotes the frequency of prescribing a given antibiotic relative to the frequencies of prescribing all antibiotics for an infection type in question expressed as a percentage.

Rational/irrational prescribing of antibiotics

- "**rational antibiotic prescribing**" used interchangeably with appropriate prescribing of antibiotics to refer to prescribing of antibiotics in ways that the prescribers were considered keeping to principles of antibiotic prescribing as they write antibiotic prescriptions.
- **"Irrational antibiotic prescribing**" used interchangeably with inappropriate prescribing of antibiotics to refer to prescribing of antibiotics in ways that the prescribers were considered not keeping to principles of antibiotic prescribing as they write antibiotic prescriptions.

Registered nurses

Refers to persons who have undergone training and obtained prescribed qualifications in nursing in institutions approved by the Lesotho Nursing Council and are registered as nurses by Council in the relevant parts of the register of nurses (LES, 1998:106,107, 112,115,116).

Relative/percentage frequencies

Used alternatively in all instances to mean the frequencies or counts of observations in given categories relative to the total frequencies or counts of all observations in all categories expressed as a percentage.

Respiratory tract infections

Disease conditions of the respiratory system denoted by specific diagnoses, symptoms or symptom complexes as sourced from patient case notes and listed in Table 4.1.12 to indicate bacterial infections or possible bacterial infections of organs and structures of the system for which antibiotics were prescribed for treatment.

Rural area

Rural areas encompass areas remotely removed from town settlements or cities in which a study site HSA hospital is located and are served by health centres or clinics that operate within the administrative and service jurisdiction of the given study site HSA hospital.

Site of infection / anatomical site of infection

The terms were used interchangeably to refer to an anatomically distinguished part of the body that has been infected by microbial agents.

Skin and soft tissue infections

Infectious diseases conditions of the skin and soft tissues respiratory system denoted by specific diagnoses, symptoms or symptom complexes as sourced from patient case notes and listed in Table 4.1.12 to indicate bacterial infections or possible bacterial infections of organs and structures of the system for which antibiotics were prescribed for treatment.

Study site

Refers to a confined area which could either be a hospital or a health service area, where data had been collected for this research.

Surgical consultants:
The term means surgeons with specialist qualifications in surgery.

Symptom complex
Combination of symptoms prescribers indicate as demonstrating presence of an infection.

Total costs of treating infection
The term refers to the total of costs of antibiotic treatment, costs of hospitalization and costs of culture sensitivity tests, if performed.

Treatment success rate (TSR)/Relative treatment success rate
Used in the context of determining the effectiveness of antibiotic prescriptions given in the treatment of infections "Treatment success rate" refers to percentage proportion of a given group of patients positively responding to antibiotic treatment with antibiotic prescriptions assessed in this study. "Relative treatment success rate" is the determined treatment success rate of a subgroup of the study population expressed relative to the treatment success rate of the study population.

Treatment outcome
The term refers to results of antibiotic treatments received by patients. In the context of this research It is defined within the provisions of meanings given to the terms "improved" "not improved" or "died" as indicators for determining the effectiveness of antibiotic treatments offered a patient.

Urban area
An urban area within the context of this study refers to the town settlement or city where a study site HSA Hospital is situated.

Workload
Refers to volume of work doctors and nurses undertake as clinicians and hence prescribers of antibiotics in both inpatient and outpatient departments of health establishments where they work and is defined by the number of patients such prescribers see within working hours stipulated by prescribers' employers.

CHAPTER ONE

1.0 STUDY OVERVIEW

1.1 INTRODUCTION

This thesis primarily focuses on antibiotic prescribing practices in public health institutions in Lesotho. Lesotho is an exemplary developing country in Africa where lack of adequate financial resources (World Bank, 2008:1) poses challenge to prescribers' expedient use of a limited number traditional or older generation antibiotics to achieve infectious disease treatment goals while forestalling the development of microbial resistance to these antibiotics. For its objective the thesis, in a situation analysis oriented type of research,

- assesses the appropriateness of antibiotic prescribing based on prescribers' adherence to principles of antibiotic prescribing;
- assesses the impact of established patterns or degrees of appropriateness of antibiotic prescribing on patients' response to antibiotic treatment;
- assesses costs of treating infections with antibiotics prescribed appropriately or inappropriately;
- identifies commonly isolated bacterial pathogens and their sensitivity patterns to antibiotics in use in hospitals selected for this study;
- assesses the effectiveness of antibiotics used in treating infections at study site hospitals.

The thesis also aims at providing rationalised baseline information developed into a formula that can be used in quantifying the therapeutic and cost properties of antibiotics to enable their selection for appropriate empiric treatment of infections. This introductory chapter provides background information on Lesotho to justify its classification as a developing country. The problem statement, outlines of the research questions and research objectives as well as an overview of the research methodology and chapter divisions are also included.

1.2. BACKGROUND AND PROBLEM STATEMENT

Empirical antibiotic therapy, defined as *the prescription of antibiotics based on clinical*

diagnosis without support of a bacteriology report (Lim *et al.*, s.a:2) or *prescribing antibiotics when there is suspected or definite infection but the causative organisms are not known* is done commonly in medical practice (Ministry of Health, 2000:5). Such prescriptions, though often ordered in the management of acutely ill patients with infections pending the outcome of culture sensitivity tests, are most often given for complete courses of treatment, particularly in hospital outpatient departments (Archer & Polk, 2005:797). The authors further indicated that the choice of an agent in such treatment options is guided by results of studies identifying the usual pathogen at the site of infection or in the clinical setting, by pharmacodynamic considerations and by the resistance profile of the expected pathogens in the particular hospital or geographical area. From these, it is obvious, that successful and cost-effective treatment of an infection in which the antibiotics being used are empirically prescribed, would largely depend on correct diagnosis and the prescriber's competency in making antibiotic choices based on his knowledge about the infection and the antibiotics at his disposal. Bosker (s.a:1), noting the difficulties of appropriate empiric prescribing of antibiotics, indicated that making antibiotic choices for such purposes is a challenging task. According to the author, it draws largely on a number of factors. Among these he mentioned the clinical experience of the prescriber, the range of available antibiotics to choose from and also referred to issues fundamental to maximising cure rates. Chambers (2001:1146) and Atif *et al.* (2000:259) also hold similar views as Bosker, (2004:1). According to these authors, prescribers need to have previous knowledge on the types, morphological characteristics and sensitivity patterns of pathogens akin to the locality in which the infection has been contracted. Inappropriate selection or injudicious use of antibiotics is a recipe for the development and spread of antibiotic resistant strains of pathogens (Chambers, 2001:1146). It results in treatment failures and serves as a drain on drug budgets of health institutions (Lim *et al.*, s.a:2; Ministry of Health, 2000:4).

Classified by world ranking as a developing country (World Bank, 2008:1) Lesotho, the selected country for this study, is a typical resource limited country for which judicious management of resources is considered mandatory for its development and the sustenance of its health delivery system. This underscores the need to conduct this research, which has the purpose of both establishing patterns of antibiotic prescribing and providing baseline information required in antibiotic policy formulation for prudent

and economic use of antibiotics in the country. This class of drugs, as indications in Table 1.2 show, takes a very significant proportion of drug budgets of the country's health institutions.

Health delivery policy formulation and administration in Lesotho take into account the socio-economic status of the nation (Ministry of Health and Social Welfare, 2000:6). As a strategy for developing a health and social services sector that will benefit its remote populations as well as address a seemingly perennial problem of shortage of doctors, the country in 1979 adopted a primary health care (PHC) system that introduced the Nurse Clinician (NC) and Community Health Worker (CHW) cadres into the health delivery system (Ministry of Health and Social Welfare, 2000: 6). These cadres are involved in drug distribution in one way or the other, with nurse clinicians at the health centre level of the PHC system being allowed to prescribe some antibiotics (Ministry of Health and Social Welfare, 2006: 9,10).

The nation also adopted a system of the health service area model of health care delivery which divided the country into 18 health service areas (HSAs). Each of these HSAs constitutes a geographic boundary to which a catchment population is ascribed. Within each HSA is a hospital owned either by Government or the Christian Health Association of Lesotho (CHAL). According to a communication with Mrs Ntholi, the Executive Secretary of CHAL, (2009), the association administratively runs all mission health facilities in the country. This includes eight hospitals and seventy-two health centres that are owned by six member churches of the association. The HSA hospitals, according to the Executive Secretary, play supervisory roles to a number of health centres (HCs) operating under them and also serve as the highest level of referral within each HSA. The Queen Elizabeth II (Queen II) Hospital in Maseru has a dual function, serving as an HSA hospital for the Maseru HSA as well as the National Referral Hospital to which cases from all other HSA hospitals that need specialist management are referred. The total bed capacity of all HSA hospitals is 2468 (Ministry of Health and Social Welfare, 2002: 4).

Currently estimated at 1:20,000 (United Nations, 2003: 33), and compared to the WHO acceptable ratio of 1:1000 (Assisi, s.a:1) the doctor-to-patient ratio in Lesotho is very

low. This situation, it is presumed, has given cause to the involvement of non-medical health professionals in the clinical management of patients. This and other factors, coupled with the absence of specific guidelines for the prescription of antibiotics in the country's health institutions, are thought to give rise to antibiotic prescription writing in the country being largely done empirically and most probably inappropriately. Present treatment guidelines (Ministry of Health & Social Welfare, 2006: 1-173) provide information on antibiotics and their doses to be used in treating given infections but do not include diagnostic algorithms (*guidelines on diagnostic procedures*) to be followed in establishing the absolute presence of bacterial pathogens as aetiological agents of said infections before decisions are made to prescribe the drugs

Antibiotic prescribing guidelines inclusive of diagnostic algorithms are particularly thought to be useful in a health care system of the type operating in Lesotho in which non-medically trained health professionals are allowed to prescribe antibiotics. In its final report on the Lesotho Pharmaceutical Sector Review, the HERA Consultancy noted that prescribing of antibiotics is based on symptoms rather than on diagnosis. Raising concern about the over-use of antibiotics in the country, the consultancy noted that on average every second prescription written in any of the various health facilities contained at least one antibiotic. This, the consultancy reported, was true for prescriptions written by both medical doctors and nurse clinicians (HERA Consultancy, 2003: 6). By interpretation of what the consultancy report entails, 50% of prescriptions emanating from various health facilities can be said to contain at least one antibiotic. This percentage of prescriptions is far more than a calculated 30% outpatient clinic attendance for infectious diseases in the country's hospitals (Table 1.1). The disparity of the two percentages is indicative of antibiotic prescribing for clinical cases that are not necessarily bacterial infections as the consultancy report purports.

Table 1.1 Total outpatient department (OPD) attendance by disease classification for all Hospitals in Lesotho (Source: Ministry of Health and Social Welfare, 2002: 9,10)

DISEASE	NO. OF ATTENDANCE		
	Governmental Hospitals	CHAL Hospitals	Totals
Coughs and colds	29435	2969	32404
Pneumonia	4642	1658	6300
Urinary Tract infection	3818	1577	5395
Pelvic inflammatory Disease	3473	1577	5050
Bronchitis	3296	1184	4480
Gonorrhoea	3510	504	4015
Syphilis	1486	252	1738
Typhoid	143	139	282
Meningococcal meningitis	35	7	42
Whooping cough	2	1	3
Anthrax	1	0	1
Urinary Tract Infections	10004	2184	12188
Total infectious cases	**59745**	**12052**	71797

Total Outpatient attendance for all cases 240027
Percentage attendance for infectious cases 30%

A number of student research project reports compiled by the Department of Pharmaceutical Technology of the country's National Health Training College (NHTC), dealt with the prescribing and usage of antibiotics at the Queen II Hospital (Marabe, 1994:6; Hoohlo, 1994:39; Tlali, 2001:6; Phalima, 2003:15). An examination of raw data collected in these studies provided useful information on problems associated with inappropriate antibiotic prescribing at the Queen II Hospital. In absence of any published work on antibiotic usage in Lesotho, these are cited here for reference. Tlali (2001:6) in one such study reported that 60% of all cases of common cold treated with antibiotics lacked evidence of bacterial infection. In another study dealing with the pattern of antibiotic indications for inpatients, Marabe (1994:6) noted that the writing of antibiotic prescriptions for inpatients in all wards of the hospital was largely inappropriate. For 78.9% of the cases in which ampicillin was used, her study noted that, the antibiotic was empirically prescribed. The study did not only identify ampicillin as the most indiscriminately used of all antibiotics at the hospital but it also presented data that expressed scepticism about the success rate of its use. This scepticism was given some credence by the results of a concurrent study (Hoohlo, 1994: 39) that investigated the sensitivity pattern of commonly isolated bacterial pathogens at the hospital. This study reported ampicillin as the antibiotic to which organisms exhibited the highest incidence

(67%) of resistance (Hoohlo, 1994: 39). In a similar study conducted in 2003, Phalima (2003:15) compiled data on culture sensitivity test results from the microbiology laboratory at the Queen II Hospital. He used a sample size of 480 bacterial isolates. An analysis of this data demonstrated that bacterial resistance to ampicillin within the sample size studied was about 82%. Within the limitations of these studies, the findings of the Marabe, Hoohlo and Phalima studies could be accepted as curtain raisers on the problems of inappropriate antibiotic prescribing and usage at the Queen II Hospital and probably other public health institutions in Lesotho. They suggest a high rate of bacterial resistance among the Basotho population and which could be a consequence of indiscriminate prescribing and use of antibiotics.

Antibiotic over-prescribing or misuse is not akin to Lesotho. It is a global problem that has drawn attention of health authorities in many countries because of its adverse bearing on the development of bacterial resistance and health care costs (Health Technology Assessment Unit, 2002:8). Chetley (1993:56), writing on antibiotic crisis as a contribution to problem drugs noted that in Nigeria, one study found 33% of antibiotic prescriptions in government hospitals and private hospitals to be inappropriate. In the same paper the author indicated that antibiotic over-prescribing was identified as a problem in the Middle East, a problem he specified as results of imprecise diagnosis and lack of confidence on the part of prescribers. He also noted that in Kuwait there had been a call for better research on patterns of antibiotic resistance and stricter controls on antibiotic prescribing and dispensing (Chetley, 1993: 56). Studying antibiotic prescribing patterns in Saudi Arabia, Abdul-Hady (1998:22) established the case of an antibiotic overuse in primary health care centres. He advocated the implementation of antibiotic policy for the management of common diseases, especially acute respiratory tract infections in that country. In another study, Denno *et al.* (2002:233), in determining the prevalence of pneumococcal colonisation and antimicrobial susceptibility among children in urban Ghana noted the emergence of *Streptococcus pneumoniae* resistance to penicillin and other commonly available antibiotics, notably co-trimoxazole and tetracycline. They recommended a curtailment of the misuse of antibiotics by prescription or otherwise to prevent further increases in resistance rates without, however, indicating how such a curtailment could be done.

Total recorded expenditure on drugs in Lesotho in the financial year 2001/2002 was R42m and provided 18.1% of the total recurrent health expenditure (HERA Consultancy, 2003:32). An analysis of drug consumption data provided by the Queen II Hospital for the period commencing January 1988 and ending December 2002 indicated that the hospital's consumption of antibiotics during these years was about 45% of its total annual expenditure on drugs (Table 1.2). A breakdown in the computer system by the end of December 2002 and which had still not been restored at the time of data collection to determine antibiotic consumption patterns as reported above, resulted in the abandonment of the electronic data capture system and hence the availability of a more recent data for this analysis. If it is assumed that antibiotic prescribing and usage in other public institutions in the country is of a pattern similar to that of the Queen II Hospital, then one could estimate that of the R42m spent on drugs in the 2000/2001 financial year according to the HERA Consultancy (2003:32) report, as much as about R18.9m was spent on antibiotics alone. This is a staggering figure that underscores the need to streamline the usage of antibiotics in the country for purposes of eliminating waste and ensuring a cost-effective treatment of infectious and communicable diseases.

Table 1.2 Queen Elizabeth II Hospital annual drug consumption data 1999-2002

Drug Expenditure analysis	YEARS					Average
	1998	1999	*2000	2001	2002	
Total Expenditure (M)	M4,143,298.00	M5,124,075.40	M1,731,469.33	M3,093,540.00	M5,042,679.00	M4,350,898.10
Expenditure on antibiotics (M)	M1,876,953.23	M2,262,675.45	M1,111,199.24	M1,242,064.31	M2,583,244.02	M1,991,234.25
Percentage Expenditure on antibiotics	45.30	44.15	*64..21	40.15	51..22	45..21%

* Consumption data for 2000 not comparable with other years and hence not used in average computations. Missing data suspected

1.2.1. Research questions

The following research questions can be formulated according to statements on problems associated with antibiotic prescribing and use in Lesotho as discussed above

- What factors mostly influence prescribers' choice of antibiotics?

- What are the commonly seen cases of infections at study sites for which antibiotics are prescribed?
- What bacterial pathogens are associated with infections commonly seen at study sites?
- What are the sensitivities of bacterial isolates to available antibiotics?
- What have the observed changing patterns in the sensitivities of bacterial pathogens been over recent years?
- What antibiotics are used routinely in treating commonly diagnosed infections?
- How effective are current patterns of antibiotic prescribing in treating diagnosed infections?
- To which degree are antibiotics appropriately prescribed at study sites?
- What is the impact of appropriate and inappropriate prescribing of antibiotics, based on prescribers' adherence to principles of antibiotic prescribing, on treated outcomes and costs of infectious disease treatment at study site hospitals?

1.3. RESEARCH OBJECTIVES

The research objectives of the empirical investigation are stated under general and specific objectives.

1.3.1 General research objectives

The general research objectives of this study were:

- to investigate and establish prescribing patterns of antibiotics in Lesotho public health institutions; and
- to demonstrate the possible effectiveness of patterns of antibiotic prescribing as established in light of current sensitivity patterns of bacterial pathogens to formulary antibiotics in the country's hospitals.

1.3.2 Specific research objectives

The specific research objectives of the literature review and empirical study included the following:

1.3.2.1 Literature Review

Literature was reviewed for a recap on the theoretical basis of antibiotic selection and prescribing in treating bacterial infections. Specifically information was sought in the literature to determine or document

- the nature of bacterial pathogens, their modes of infections and diseases associated with them;
- essential characteristics, mechanisms of action and current developments in the use of antibiotics;
- mechanisms of bacterial pathogen antibiotic resistance development and the role of antibiotic prescribing and use in such resistance development;
- principles of empiric rational antibiotic selection and prescribing;
- methods of antibiotic prescription rationality assessment;

1.3.2.2 Empiric research

The empiric research study had the following specific objectives:

i. To establish extents to which antibiotics are prescribed appropriately in inpatient and outpatient settings in public health institutions in Lesotho through prescribers' adherence to principles of antibiotic prescribing.
ii. To determine the impact of appropriateness of antibiotic prescribing on treatment outcomes and costs of antibiotic treatment.
iii. To determine in terms of monetary value the proportions of prescribed antibiotics wasted on account of their inappropriate prescribing for cases identified as not having infections.
iv. To determine the extent of multiple prescribing of antibiotics in inpatient and outpatient settings and the impacts of same on treatment outcomes.
v. To establish infections commonly diagnosed and antibiotics most frequently prescribed in their treatment in both inpatient and outpatient departments.
vi. To predict effectiveness of established patterns of antibiotic prescribing in treating infections or preventing post surgical wound infections in inpatients and outpatients.
vii. To determine prescriber qualifications involved and their abilities in prescribing antibiotics appropriately in outpatient departments.

viii. To determine the impact of antibiotic stock unavailability on prescribers' choice of antibiotics in outpatient departments.

ix. To determine the extent to which prescribers establish patients' need for antibiotics before prescribing the drugs in outpatient departments.

x. To evaluate the extent of accuracy of prescriber diagnosed infections and the effects of same on appropriateness of antibiotic prescribing in outpatient departments.

xi. To determine the extent of bacterial pathogen isolations at study sites.

xii. To determine and provide a list of bacterial pathogens associated with commonly diagnosed infectious diseases in Lesotho for adequate antibiotic coverage in empiric treatments of infections.

xiii. To determine sensitivity patterns of bacterial pathogens to prescribed antibiotics.

xiv. To determine any changes in bacterial sensitivity patterns to given antibiotics over the past five years preceding the period of sensitivity data collection.

xv. To develop an easily applicable procedure for the rational antibiotic selection in the treatment of infections based on available data on frequencies of isolation of pathogens from given specimens, their sensitivities to formulary antibiotics and the costs of antibiotics indicated for the treatment of their infections.

xvi. To establish factors contributing to established patterns of antibiotic prescribing in Lesotho as determined according to the following:

(a) Prescribers' levels of professional training, work experience, and workload.

(b) Availabilities and functional capabilities of support systems required in antibiotic prescribing.

(c) Influences of patient and prescriber-related factors on prescribers' decisions to prescribe antibiotics.

(d) Extent to which prescribers adhere to principles of antibiotic prescribing.

(e) Reasons for prescriber's non-request for laboratory assisted information in appropriate prescribing of antibiotics.

(f) Prescribers' knowledge as a pre-requisite in appropriate prescribing of antibiotics.

(g) Costs of antibiotics and pathogen sensitivity pattern considerations in making appropriate choices of antibiotics.
(h) Antibiotic stock unavailability as a factor influencing respondents' ability to select antibiotics of choice.

1.4 Research design and methodology

1.4.1 Research type

The first phase of the research (Phase I) was an observational pharmacoepidemiological type of study designed in a case series study format (Waning & Montagne, 2001: 50). Case reports for individual patients treated for infections were prospectively collected over a specified period in hospital wards and outpatient departments at five (5) study site hospitals. Data for the characterisation of antibiotic sensitivity patterns of commonly isolated pathogens for the second phase of the research were on the other hand retrospectively collected from culture sensitivity test result records for a five and a half year period from the medical laboratories of study site hospitals. A questionnaire survey method of data collection in which questionnaires were hand delivered and collected from centralised points was employed in collecting data for analysis in a third phase of the research.

1.4.2 Study sites

Five Health Service Area (HSA) hospitals comprising three government and two Christian Health Association of Lesotho (CHAL) hospitals were selected on purpose on account of their sizes and operational policies which made them a convenient sample of acceptable representative hospitals. Government and CHAL hospitals are the two types of public sector hospitals that operate in the health care delivery system of Lesotho. Criteria used in their selection as study sites for the research were based on their size in terms of number of patient beds they accommodate and their ease of accessibility to the researcher. The inclusion of two of the country's biggest hospitals which are Government owned, that is the Queen Elizabeth II (Queen II) (450 beds) and the Motebang hospitals (287 beds) as well as the Maluti hospital (150 beds) which also is the biggest among the CHAL hospitals was intended to make an acceptable extrapolation of results obtained to that of the country situation. The rest of the selected

hospitals were the Berea government hospital (128 beds) and the Scott hospital which is a CHAL hospital with a bed capacity of 102.

1.4.3 Research methodology

The research was carried out in two stages with the first embodying a literature study and the second, an empirical study in which the following were done.

- Assessment of antibiotic prescriptions and their cost from inpatient and outpatient departments of study site hospitals (Phase I).
- Investigation of sensitivity patterns of pathogens to prescribed antibiotics often prescribed for infections at study sites (Phase II).
- Investigation of factors that most likely contribute to observed patterns of antibiotic prescribing (Phase III).

1.4.4 Literature study

Books, journals and publications were reviewed for compilation of relevant information in line with the specific objectives with particular focus on the characterisation and pathogenesis of bacterial pathogens, types and uses of antibiotics, and principles of antibiotic prescribing as outlined above in Section 1.3.2.1

.

1.4.5 Empirical Study

A stepwise approach in data collection, as indicated below, was followed during the empirical study. Various data collection tools were developed and along with literature-derived fact sheets about clinical conditions for which antibiotics were prescribed, formulary antibiotics and commonly isolated bacterial pathogens from study site hospitals were used at each step of the data collection. The tools were designed to provide information needed in addressing the research questions. All tools were adequately tested to ensure their suitability for the study before their use. They are summarised below in Table 1.3.

Phase I

Relevant data on prescribed antibiotics were collected from patients' medical records from the outpatient departments and all wards, medical and surgical, at each study site hospital, namely, Berea, Maluti, Motebang, Queen II and Scott hospitals, using data collection tools 1 and 2 (Appendices 1 and 2). Data collection period was for one month

commencing June 15, 2006 and ending July 15, 2006. Senior pharmacy students in training at study site hospitals were trained and engaged as research assistants in the collection of data. The period of data collection was decided on for reasons of it being

Table 1.3 Data collection tools (DCT) and guidelines: Their purposes and appendix references.

Tool number	Purpose	Appendix Reference number
DCT-1	Collection of data on individual inpatients	1
DCT-2	Collection of data on individual inpatients	2
DCT-3	Summarisation of data on inpatient prescription conformity to criteria set for prescription rationality rating	3
DCT-4	Summarisation of data on outpatient prescription conformity to criteria set for prescription rationality rating	4
Guideline	Provision of guidelines in determining absolute presence, suspected presence or absence of bacteria as aetiological agents of infections	6
Guideline	Provision of guidelines in determining spectra of activity of prescribed antibiotics	7
DCT-5	Summarisation of inpatient antibiotic treatment costs	8
DCT-6	Summarisation of outpatient antibiotic treatment costs	9
DCT-7	Collection of data on sensitivities of bacterial pathogens to prescribed antibiotics	11

Abbreviation:
DCT: Data collection tool

the vacation period of the students engaged in the data collection process. Data collected were derived from case reports for individual patients treated for infections.

Criteria for categorising antibiotic prescriptions into groups were developed according to their appropriateness for both inpatients and outpatients based on literature documented principles of rational antibiotic prescribing. They were formatted into tabular questionnaire type of data collection tools (Appendices 3 and 4). Patients' records were examined and information on whether given antibiotic prescription records met set criteria or not were collected for both inpatients (Appendix 3) and outpatients (Appendix 4) using these tools. Information was compiled from the literature for purposes of making decisions, where necessary, on the conformation of antibiotic prescriptions to set criteria used in their assessment (Appendices 5 and 6). Data collection tools 5 and 6,

(Appendices 7 and 8) were developed and used to summarise information on costs of prescribed antibiotics for both inpatients and outpatients.

Phase II

Data on the sensitivity patterns of commonly isolated pathogens to available antibiotics on culture sensitivity test results were collected retrospectively at study sites using data collection tool 7 (Appendix 10). Data collection covered a five and a half-year period, extending from January 2000 to June 2006. Data collected were analysed to establish sensitivity trends of pathogenic bacteria to available antibiotics and their associations with diseases and sites of infections.

Phase III

Data for investigating factors contributing to established patterns of antibiotic prescribing were collected using questionnaires designed for the purpose [data collection tool no. 8 (Appendix 13)]. Said questionnaires were given to doctors and nurse prescribers in the five HSAs whose hospitals were used as sites for Phase I of the empiric study to respond to.

1.4.6 Data analysis

Data were analysed descriptively or by inferential statistics where appropriate to establish trends and cost and treatment outcomes of antibiotic prescriptions and determine the practical significance of results. For comparative purposes analysis of data was done to reflect antibiotic prescribing trends at individual study sites. Data from all study sites were pooled and analysed to reflect the country situation.

All data collected and summarised were electronically captured in Microsoft Excel® 2007 and imported into Statistical Analysis Systems® SAS for Windows 9.1® programme for analysis in accordance with set objectives of the research.

1.4.7 Study samples

Patient prescription records from both outpatient and inpatient departments as well as laboratory sensitivity test result records at study sites constituted the subjects of study for the research.

1.4.7.1 Antibiotic prescription data – Phase I of empiric study

All antibiotic prescriptions emanating from inpatient (N = 307) and outpatient (N = 865) departments at study sites during the one month study period from June 15, 2006 to July 15, 2006 in the exception of prescription records meeting sample exclusion criteria as indicated in Section 1.4.7.4 below were entered into study.

1.4.7.2 Culture sensitivity test result data – Phase II of empiric study

All laboratory culture sensitivity test result records (N = 5007) spanning retrospectively from January 1, 2000 to July 31, 2006 constituted the study samples for this step of the study.

1.4.7.3 Factors contributing to established patterns of antibiotic prescribing - Phase III of empiric study.

Study samples for this step of the research included all questionnaires returned from respondents (n = 51) made up of doctors and nurses involved in antibiotic prescribing at study site HSAs.

1.4.7.4 Inclusion and Exclusion Criteria

All patient records with prescriptions for antibiotics were included in the data collected for analysis within the stated period of this research in the exception of those of patients in the advanced stage of human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS). This patient group was excluded on the basis of unpredictable treatment outcomes of antibiotic treatment in them as reports of a number of studies indicated. Feikin *et al.* (2000:224,226) in their study of "*invasive pneumococcal pneumonia in the era of antibiotic resistance*" indicated that the presence of severe underlying disease is a factor that consistently predicts mortality from invasive pneumococcal pneumonia. On account of this reason, they grouped their study subjects with HIV/AIDS among those with severe underlying disease for different assessment. According to them, however, invasive pneumonia is not increased among patients with HIV infection without AIDS. Rolain *et al.* (2004:1921) reported that the pathological response to infection with *Bartonella* spp varies substantially with the status of the host immune system. Connolly *et al.* (1988:595) commented on their notices of erythromycin reducing severity of diarrhoea in 5 out of 9 but producing nausea, vomiting and abdominal pain in the rest of study subjects in a study in which they investigated

treatment options in HIV/AIDS patients with cryptosporidial diarrhoea. They also reported on 2 out of 4 such study subjects not responding to erythromycin but to either spiramycin or clindamycin treatment, though with more severe side-effects. The above mentioned studies highlighted the unpredictability of what one would expect as antibiotic treatment outcomes in patients with HIV/AIDS.

1.5 Results reporting

Results of the study were reported in Chapter 4 in table formats supported where necessary with descriptive statistical graphs.

1.6 Ethical permissions

Ethical permissions were both sought from the Ministry of Health of Lesotho through its ethics committee for public hospitals and individual CHAL hospitals (Appendices 18, 19 and 20) as required as well as the ethics committee of the North-West University (Number 06K17) for the conduct of this research.

1.7 Chapter divisions

The write up of the research thesis is divided into five (5) chapters captioned as follows:

Chapter 1 Overview
Chapter 2 Bacterial pathogens, antibiotics and principles of antibiotic prescribing
Chapter 3 Research methodology
Chapter 4 Results and discussions
Chapter 5 Conclusions and recommendations

1.8 Chapter Summary

A complete overview of the study was presented in this chapter. Background information and statement on the problem necessitating the study were highlighted and so also were the study design, conduct and set objectives. The literature as reviewed to provide the information needed for understanding the subject matter of investigation as enshrined in the study is presented in the next chapter.

CHAPTER TWO

2.0 BACTERIAL PATHOGENS, ANTIBIOTICS AND PRINCIPLES OF ANTIBIOTIC PRESCRIBING

The chapter reviews general knowledge considered important to the understanding of principles required for making appropriate choices of antibiotics as well as the theoretical basis of the design of this research in accordance with specific objectives set for this study. It contains a discussion of types and characteristics of bacterial pathogens, mechanisms of their pathogenesis and resistant development to antibiotics, infectious diseases they are associated with and patterns of their sensitivities to antibacterial agents. Available literature on most commonly used and more recent antibacterial agents has also been reviewed and fact sheets prepared in tabular format on the various types and classifications of the drugs. This review was done with the objective of providing information one would need in making informed therapeutic decisions on antibiotic choices. Areas of information provided covered accordingly, the classification and characteristics of the various antibiotics considered, the mechanisms of actions and microbial development of resistance to their use, their spectra of antibacterial activity and therapeutic applications and their adverse effects and interactions with other drugs. Principles of antibiotic prescribing as applied in the design of the methodology of this study were also reviewed, so also were methods commonly employed in studies involving the assessment of the appropriateness of antibiotic prescriptions. The merits and demerits of such methods were considered and a justification for basing the appropriateness assessment of antibiotic prescriptions on prescribers' adherence to principles of antibiotic prescribing as employed in this study was provided.

2.1 Bacterial pathogens: Morphological characteristics, classification and mechanisms pathogenesis

Bacterial pathogens by definition of Elliot *et al.* (2004: 155) refer to bacteria that have the potential of causing an infection in a host following colonisation. They may be commensals in the host at one point in time but may turn into pathogens at another time, depending on prevailing situations. *Neisseria meningitidis* for example is a commensal of the pharynx in about 5% of adults but is also an important pathogen that causes meningitis. *Streptococcus pneumoniae* is similarly the most frequent cause of bacterial

pneumonia in humans but is at the same time a pharyngeal commensal in many individuals and so also is *Staphylococcus aureus* which is an important cause of skin infections and deep abscesses but is a nasal commensal in about one third of individuals (Elliot *et al.* 2004: 155).

2.1.1 Cell wall structure and staining characteristics

Bacteria maintain their shape by a strong rigid cell wall. Based on differences of their cell wall structure and reactions to staining agents bacteria can morphologically be differentiated from one type to another. Depending on their reactions with Gram's staining reagents, bacteria can be divided into two major groups, namely gram-positive and gram-negative bacteria (Wilson *et al.*, 2002 217; Elliot *et al.*, 2004: 1&2). When treated with Gram's stain, gram-positive bacteria become stained blue/black and gram-negative bacteria, red (Elliot *et al.*, 2004: 1&2).

A comparison of the structure and composition of gram-positive and gram-negative bacteria cell walls is shown in Figure 2.1. Structurally gram-positive bacteria have a thick cell wall composed of layers of peptidoglycan units of about 50 -100 molecules in thickness. Peptidoglycan is a complex molecule composed of linear strands of two alternating amino acid sugars (N-acetylglucosamine and N-acetylmuraminic acid) that are cross linked by peptide chains (Marerro *et al.,* 2006:507). Also present are other cell wall components such as teichoic acid. Underneath the cell wall is bilayer phospholipid cell membrane in which proteins are embedded with some, like penicillin binding proteins (PBP) and porins (proteins forming water channels), spanning the membrane (Petri, 2001: 1190). Gram-negative bacteria differ structurally from gram-positive bacteria. They are composed of an outer and an inner cell membrane between which is a thin peptidoglycan layer of about 1 or 2 molecules in thickness (Petri, 2001:1190). The outer lipid membrane bilayer is spanned with porins. Gram-negative bacteria's outer cell membranes also characteristically contain lipopolyscaccharides or endotoxins which contain toxic components which, when released on cell lysis, are involved in the pathogenesis of this class of bacteria (Elliot *et al.*, 2004:3; Wilson 2002:217).

Some bacteria have in their cell walls a waxy layer which prevents permeation of dyes and organic solvents. They are not stained with Gram staining reagents and need special staining techniques such as the Ziehl Nelsen method to get them stained for

microscopic identification (Inglis, 2003:10). This involves the staining of heat fixed micro-organisms on microscope slides with hot carbol-fulcin dye which stains all bacteria and then decolourising by washing the slide with 20% sulphuric acid. Bacteria resisting discoloration when washed with the acid are typed as acid fast bacteria (Elliot *et al.*, 2004:170).

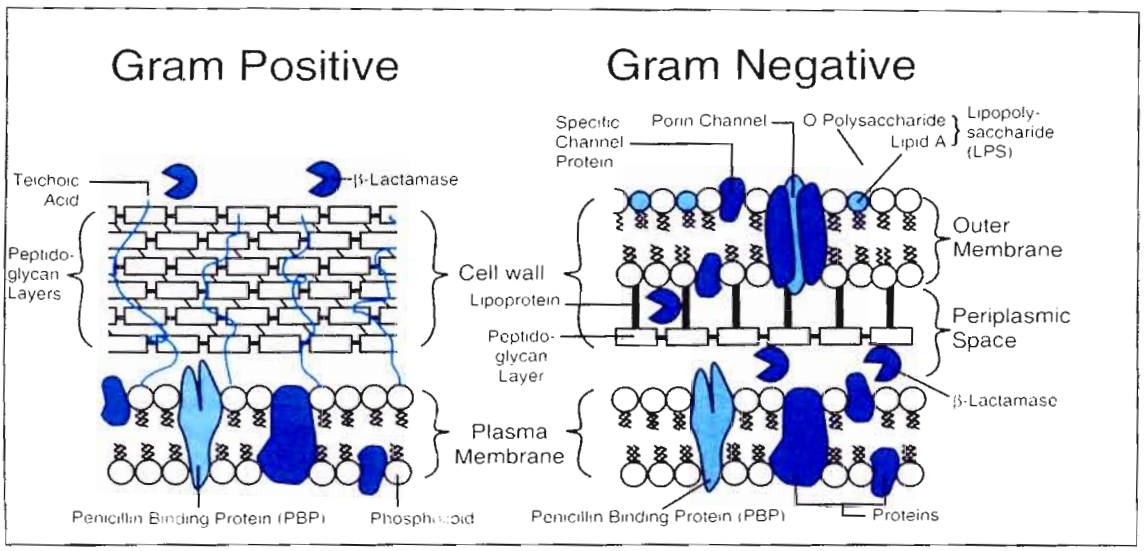

Figure 2.1 Comparison of the structure and composition of Gram-positive and Gram-negative bacteria cell walls (Adapted from Petri, 2001:1191)

2.1.2 Morphological classifications

Elliot *et al.* (2004:20) divided medically important bacteria into five main groups that included gram-positive, gram-negative, acid fast, spiral and cell wall deficient bacteria. Morphological identification is based on the shapes of individual cells and colonies they form on growth media. Colour reagent staining properties used for purposes of identification or classification are results of bacteria cell-wall colour reactions with Gram or acid fast stains as reviewed above. Examples of five main groupings of pathogenic bacteria according to classification in (Elliot *et al.*, 2004:20) are listed with major group examples as indicated below.

2.1.2.1 Gram-positive bacteria

They comprise as indicated below with major group examples, cocci, bacilli and branching bacteria.

- **Gram-positive cocci** exemplified by *Staphylococcus* spp (e.g. *S. aureus, S.epidermidis, & S. saprophyticus)*) which show as cluster colonies on growth media; *Streptococcus* (*S. pneumoniae, S. pyogenes*) and *Enterococcus* spp (e.g. *E. faecalis*) which are seen as chains or in pairs on growth media; *Micrococcus* spp which form square colonies and *Peptococcus* and *Peptostreptococcus* spp which grow in chains (Elliot *et al.*, 2004:21). Gram-positive bacteria generally grow in the presence or absence of oxygen and are described as facultative bacteria. This is in exception of *Peptococcus* and *Peptostreptococcus* spp which are obligate anaerobes requiring the absence of oxygen to grow.

- **Gram-positive bacilli**: Specific members of the group may be sporing, non-sporing, or branching (Elliot *et al.*, 2004:21). With respect to their oxygen requirements for growth, and as further indicated by Elliot *et al.* (2004:21) they may be obligatory aerobes or anaerobes or be facultative when they grow in both conditions. Examples include *Bacillus* spp (aerobic and spore forming) e.g. (*B. anthracis*); *Corynebacterium* spp (facultative and non-sporing) e.g. *C. diphtheriae*).; *Listeria* spp (aerobic or microaerophilic and non-spore forming) e.g. *L. monocytogenes*); *Lactobacillus* spp which may be anaerobic or microaerophilic; *Clostridium* spp which are anaerobic and spore-forming (e.g. *C. difficile* & *C. botulinum C. perfringens* & *C. tetani*); *Propionibacterium* spp (*P. acnes*) which are non-sporing and anaerobic; *Actinomyces* spp (e.g. *A. Israeli*) which are anaerobic and branch forming and *Nordcardia* spp (e. g. *N. asteroides*) which are aerobic and branch forming.

2.1.2.2 Gram-negative bacteria

The classification according to Elliot *et al.* (2004:22) and Inglis (2003:248) includes cocci, bacilli, comma-shaped and intracellular bacteria as specified below with their group examples.

- **Gram-negative cocci:** Typical examples are *Neisseria* (e.g. *N. gonorrhoeae* & *N. meningitidis*) and *Veillonella* species which are respectively obligate aerobes and anaerobes (Elliot *et al.*, 2004:22).

- **Gram-negative bacilli**: These include a group of enteric bacilli (*Enterobacteriaceae*), also referred to colloquially as "coliforms". They are facultative in their oxygen requirements for growth and are commonly found as part of the intestinal flora (Inglis, 2003:248). Examples include *Enterobacter* spp (e.g. *E. chloacea*) *Escherichia coli*, *Klebsiella* spp (e.g. *K. pneumoniae*) *Proteus* spp. (e.g. *P. Mirabilis*), *Salmonella* (*S. typhimurium*), *Serratia* spp (e.g. *S. marcescens*), *Shigella* spp (*S. sonnei.*) and *Yersinia* (*Y. enterocolitica*) (Elliot *et al.*, 2004:22; Inglis, 2003:248,249). Other pathologically important gram-negative bacilli are environmental organisms unlike the *Enterobacteriaceae*. Significant among these according to Inglis (2003:250) are *Pseudomonas spp* (e.g. *P. aeruginosa*), an obligate aerobe associated with a number of hospital acquired infections, *Burkholderia* spp (e.g. *B. pseudomallei* and *B. cepacia*) which are opportunistic pathogens in patients with cystic fibrosis; *Stenotrophomonas* spp (*S. maltophilia*), opportunistic pathogens in immunocompromised patients e.g. leukaemics, and *Acinetobacter* spp a group of gram-negative coccobacilli widely dispersed in hospital environments and are a cause of hospital acquired infections (Elliot *et al.,* 2004, 69). Other gram-negative bacilli include the *Parvobacteria* which may or may not require oxygen for their growth, depending on the species (Elliot *et al.*, 2004:57). They are fastidious requiring specific laboratory conditions for their growth. Examples include *Legionella* (e.g. *L. pneumophilia*) an obligate aerobic and, *Bacteroides* spp (e.g. *B. fragilis*) and *Fusobacterium* which are obligate anaerobic members of the group. Others are *Bordetella* spp (e.g. *B. pertusis*), *Brocella* spp (*B. abortus*), *Haemophillus* spp (*H. influenzae, H. ducreyi, H. parainfluenzae*) and *Pasteurella* spp (e.g. *P. multocida*) (Elliot *et al.*, 2004:57). Legionellaceae, typically *L. pneumophilia, L. micdadae, L. bozmanii, L. dumoffii* and *L.longbeachae* are most commonly implicated in human infections (Chang & Yu (2005:870).

- **Comma shaped or curved Gram-negative bacteria:** These are facultative in their oxygen requirements for growth. Examples include the vibrios i.e. *Vibrio* spp (e.g. *V.*

cholerae, *V. vulnificus* and *V. parahaemolyticus*), *Campylobacter* spp (e.g. *C. jejuni*) and *Helicobacter* spp (e.g. *H. pylori*) (Elliot *et al.,* 2004:63; Inglis, 2003: 251).

- **Intracellular Gram-negative bacteria:** These are generally small bacteria that require intracellular environment for their growth and are not routinely cultured in diagnostic microbiology laboratories. (Inglis, 2003: 255). Examples as indicted by the author include the following:
  - *Clamydias* of which *Clamydia trachomatis*, (causative agents for eye disease, urethritis and cervicitis and lymphogranuloma venereum), *C. psittaci* (causative agent for psittacosis, an uncommon respiratory infection) and *C. pneumoniae* (causative agent for an atypical pneumonia) are medically important members of the group include.
  - *Rickettsiae* and *Coxiellae*:
    Rickettsiae are obligate intracellular gram-negative bacteria with preference for vascular endothelium. Rickettsial diseases are associated with petechial (vasculitic rash) and multisystem disease (Elliot *et al.,* 2004:63).
    Coxiella is a related genus that causes acute disease (atypical pneumonia), and chronic disease (infective endocarditis) (Elliot *et al.,* 2004:86)

- **Acid–fast bacilli**

  Acid-fast bacteria by definitions provided in Elliot *et al.* (2004:23) and Inglis (2003: 253) include the genus *Mycobacterium*. They are slow growing and have a cell wall structure that differs from gram-negative and gram-positive species by not depending on peptidoglycan for their integrity. They have instead mycolic acid and waxes that make them resist conventional stains. They resist decolourisation with acid after being stained with hot carbol fuchsin, hence their stated morphological classification. They are basically of three types, and include the following:
  - Tubercle bacilli, comprising *Mycobacterium tuberculosis* and *M. bovis*
  - Leprosy bacilli, exemplified by *Mycobacterium leprae*
  - Atypical mycobacteria which embodies types of mycobacteria demonstrating unique properties like growth temperatures, pigment production when grown in either light (photochromogens) or darkness (scotochromogens) or rapidity of their growth. Examples include *M. kansasii*, (photochromogenic) *M. avium* and *M. intracellulare*, (non pigmented mycobacteria commonly associated with

pulmonary and extrapulmonary infections in HIV patients) and *M. chelonei*, which are fast growing.

- **Spirochaetes (Spiral bacteria)**

  These are relatively slender spiral shaped filamentous bacilli according to definitions of Elliot *et al.* (2004:23). With the exception of a few, they generally cannot be cultivated in the laboratory. They are classified into three clinically important genera that include the following according to the authors.

  - *Borrellia*, which are relatively large motile spirochaetes exemplified by *B. vicenti* and *Leptotrichia buccalis and B recurrentis*. *B. vicenti* and *Leptotrichia buccalis* are known causative agents for Vincents angina while *B recurrentis* is associated with relapsing fever.
  - *Treponema*, which are relatively thinner and more tightly coiled than *Borrelia.* Typical examples are *Treponema pallidum* and *T. pertenue*, which respectively cause syphilis and yaws.
  - *Leptospira*: These are finer and more tightly coiled than the Treponemes. They are classified as a single species of *Leptospira interrogans*. Many of their available serotypes (over 130) are pathogenic. Among these are *L. icterohaemorrhagiae* which causes Weil's syndrome, a disease characterised by jaundice, renal dysfunction and haemorrhagic diathesis (Speelman, 2005:988), and *L. canicola* which causes lymphocytic meningitis (Elliot *et al.* (2004:23) or canicola fever (Banister *et al.*, 2000:203;)

- **Cell wall-deficient bacteria**

Cell wall-deficient bacteria do not have cell walls and may be defined according to Onwuamaegbu *et al.* (2005:2), as bacteria with altered morphology and cultural characteristics consistent with damaged or absent cell wall structures. They may occur naturally or be induced in the laboratory. They are also referred to as mycoplasmas and are different from L-form bacteria. L- form bacteria, named so after Lister institute of London where this type was first described. They refer to bacteria without cell wall *in vitro* and which grow on solid media treated with penicillin. They may be considered as pleomorphic variants of bacteria with deficient wall characteristics that may require hypertonic media and may revert to walled organisms (Onwuamaegbu *et al.*, 2005:2). Cell wall-deficient bacteria occurring naturally are referred to as mycoplasmas, and are

differentiated from L. form cell wall-deficient bacteria as defined above. Pathogenic important species of mycoplasmas typically include *Mycoplasma pneumoniae* and *Ureaplasma urealyticum* (Elliot *et al.*, 2004: 23). They are not stained by gram stain reagents and are also resistant to the effects of β-lactam antibiotics because of their lack of cell wall. They cause atypical pneumonia, upper respiratory tract infections and central nervous system complications. Most isolates are sensitive to Erythromycin and Tetracycline. (Inglis, 2003: 254).

2.1.3 Mechanisms of bacterial pathogenesis

This aspect of the review deals mainly with host-microbe interactions. It describes the ability of bacteria to colonise a host and remain as a commensal or otherwise become virulent and invade host tissues to cause infection or disease. Terms used to describe these processes evolved over time as bacterial host interactions become better understood (Casadeval & Pirofsky, 2000:6511) and ambiguities do arise as these terms get applied in describing bacteria-host interactions. As a prelude to descriptions of mechanisms of bacterial pathogenesis as reviewed in sections that follow, some of these terms are discussed and defined within contexts of their usage in this study. They include the following:

Pathogen: Todar (2009: 1) defined pathogen as a microorganism that is able to cause disease in a plant, animal or insect. According to Casadeval and Pirofski (1999:3703), some microbes were classified as pathogens although they do not cause disease in every host while some microbes are classified as non-pathogens although they do cause disease in certain hosts. The term pathogen by these authors' definitions appeared to be defined relative to the microbe-host interaction being considered. Within the context of this research, the term is used to refer to bacterium that is a known causative agent of infectious disease in humans.

Bacterial colonisation, infection and disease: Bacterial colonisation refers to the adherence and initial multiplication of bacteria in the host (Todar, 2009:1). Colonisation may or may not result in infection or disease according to Casadevall & Pirofski, (2000:6516). According to the authors, colonisation is a state in which the microbe may be present in the host for a variable duration of time during which damage to the host may or may not be induced. A microbe-specific immune response is often triggered in

the host and this could in turn eradicate or contain the microbe. In such cases diseases or infections may not result from the colonisation. If the microbe is not eliminated by the host immune response, by antibiotic therapy or by vaccination, a state of persistence may ensue. Progressive damage resulting from such a state may lead to infection or disease and death of the host (Casadevall & Pirofski, 2000:6516).

Generally, processes of infection and disease are results of interactions of various microbial and host molecules (Pier, 2005:700). Such host-pathogen interactions are antagonistic relationships and for an infection to either occur or fail to occur, the ability of either host or pathogens overcoming each other in such an interactive process becomes the deciding factor (Tan *et al.*, 1999:715). In this review colonisation is used to indicate a first stage of bacterial infections in human hosts with a possibility of leading into disease.

Elliot *et al.* (2004:155) defined infections as clinical manifestations that occur when microorganisms invade a host. According to the author, when the manifestations are minor or imperceptible, infections are often termed subclinical. Latent infection they further they further indicated results when pathogens persist in the body without evoking a clinical response but with possibilities of overt infections periodically occurring following a change in the patient's immune state. Examples as given by the author included such viral infections as cytomegalovirus infection in transplant patients or herpetic cold sores that commonly occur in persons.

From indications of Pier (2005:700) and Inglis (2003:19), processes of bacterial colonisation, infection and disease occur in stages and can be classified into

- microbial encounter and entry into the host, that is acquisition of the microorganism by the host through such processes as direct contact, inhalation, ingestion, inoculation or transplacental transmission;
- microbial growth after entry or colonisation;
- avoidance of innate host defences; and
- tissue invasion and tissue tropism, which involve microbial penetration of specific anatomical barriers resulting in spread of the pathogen in the host.

Virulence: In a mini-review on the subject matter of bacterial virulence Casadevall and Pirofski (1999:3703) considered opinions of various authors (Zinsser H. 1914; Ford, 1927; Watson & Brandy 1949; Harries *et al.,* 1951; Hoeprich,1983; Lipsitch *et al.,* 1997)

and provided different versions of definitions of bacterial virulence. These included bacterial virulence being considered as the ability of the microbe to reproduce in the body (Ford, 1927); the quantitative and a qualitative property of the microbe that determines its capacity to cause disease (Watson & Brandy, 1949); and also as a property of a microbe that depends on various independent variables including the qualities of microbial aggressiveness, infectivity, toxigenicity and communicability (Zinsser H., 1914, Watson & Brandy, 1949, Harries *et al.,* 1951, Lipsitch *et al.,* 1997). Attributes identified with virulence according to Hoeprich (1983) as expressed in the authors' mini-review depended on the pathogens' invasiveness, intoxication and hypersensitivity. Toxin producing organisms such as *Clostridium tetani* had high intoxication properties by such attributes while *Staphylococcus aureus* was considered highly invasive. *Mycobacterium tuberculosis* in the same context was considered having both invasive and hyper sensitivity-eliciting properties. The association of hypersensitivity of some pathogens implied that virulence was linked with host response. Todar (2009:1) defined virulence as the degree of pathogenicity of a microbe with virulence factors characterised with the pathogen being regarded as the determinants of such degree of pathogenicity. By Todar's (2009:1) definition virulence factors can be considered as any of the genetic or biochemical or structural features that enable the pathogen to colonise and produce disease in the host. This meaning is implied any where the term is used in this review.

Bacteria pathogenicity: This is the ability, of bacteria to produce disease in a host organism according to Todar (2009:1). Pathogenicity as Casadevall and Pirofski (2000:6511) indicated is neither an invariant nor a stable characteristic of most microbes and the acquisition of pathogenic microbes is not synonymous with disease. In the clinical realm, Casadeval and Pirofski (2000:6511) noted that a microbe responsible for an epidemic disease could be isolated from both symptomatic and asymptomatic individuals in the midst of an epidemic. In support of this view, they quoted Henrici (1934) as proving that in the midst of an epidemic of cerebrospinal meningitis due to *Neisseria meningitis* in a community only a small number of individuals developed the disease and that others carried the bacteria but remained healthy. By their interpretation, pathogenicity could or could not be expressed in a host by given bacterial pathogen. In this study, bacteria pathogenicity is used to indicate the ability of a given bacteria to produce disease according to Todar's (2009:1) definition irrespective of whether it does

or does not produce disease in certain individuals as Casadeval and Pirofski (2000:6511) pointed out.

Pathogenicity islands: Wilson *et al.* (2002:220) stated that the genomic make ups of bacterial genomes are subject to rapid and dramatic change through a variety of processes collectively referred to as horizontal gene transfer. Principally, the process refers to the incorporation of genetic elements transferred from a donor organism directly into the genome of the recipient organism where they form genomic islands. Genomic islands as defined by the authors are large blocks of DNA containing mobile genetic elements. The islands according to the authors may contain mobile block of virulence determinants, e.g. adhesins, invasins, toxins, protein resistance mechanisms and are thus referred to as pathogenicity islands. Pathogenicity islands were first described in pathogenic species of *E. coli*, but are now described in a number of organisms including, *Yersinia, Listeria, Staphylococcus aureus. Salmonella, Vibrio, Shigella*. They are present in pathogenic bacterial strains but absent in the genomes of non-pathogenic members of the same or related species (Wilson *et al.,* 2002:220).

Other terms as variously used in the review pertaining to adherence factors in host - parasite interactions are compiled and defined in Table 2.1 according to Todar 2009:2.

- **Microbial acquisition by host**

The most common site of microbial entry into host is mucosal surfaces, comprising the respiratory, alimentary and genitourinary tracts, and the skin or the conjunctiva in the case of eye infections. Unbroken skin though difficult to penetrate by most pathogens becomes a good site of microbial entry into host when portals of entry like cuts, bites, burns and trauma become created on it (Pier, 2005:700).

For microbial entry through a particular site to be successful, Pier (2005:700) stated that it is necessary for the microbe in question to have specific characteristics that would permit it to survive and grow in the host tissue. He mentioned microbial entry through the alimentary tract, for example, being possible for pathogens that can survive in the varied environments of the gastrointestinal tract including low gastric pH and high bile content of the intestines. Similarly organisms gaining access through the respiratory tract he

Table 2.1: Terms used to describe adherence factors in host -parasite interactions (adapted from Todar, 2009:2)

ADHERENCE FACTOR	DESCRIPTION
Adhesin	A surface structure or macromolecule that binds bacterium to a specific surface
Receptor	A complementary macromolecular binding site on a eucaryotic surface that binds specific adhesins and ligands
Lectin	Any protein that binds to a carbohydrate
Ligand	A surface molecule that exhibits specific binding to a receptor molecule on another surface
Mucous	The mucopolysacharide layer of glucosaminoglycans covering animal cell mucosal surfaces
Fimbrae	Filamentous proteins on the surface of bacterial cells that may behave as adhesins for specific adherence
Common pilli	Same as fimbriae
Sex pilus	A specialised pilus that binds mating prokaryotes together for the purpose of DNA transfer
Type I fimbrae	Fimbriae in Enterobacteriaceae which bind specifically to mannose terminated glycoproteins on eukaryotic cell surfaces
Type 4 pilli	Pilli in certain gram-positive and gram-negative bacteria. In Pseudomonas it is thought to play a role in adherence and biofilm formation
S-layer	Proteins that form the outermost cell envelope component of a broad spectrum of bacteria, enabling them to adhere to host cell membranes and environmental surfaces in order to colonise
Glycocalyx	A layer of exopolysaccharide fibres on the surface of bacterial cells which may be involved in adherence to a surface. Some times used as a general term for a capsule of a bacterial cell
Capsule	A detectable layer of polysaccharide (rarely polypeptide) on the surface of bacterial cell which may mediate specific or non-specific attachment or according to Wilson *et al.*, (2002:216) even evade phagocytic clearance form site of infection
Lipopolysacharide (LPS)	A distinct cell wall component of the outer membrane of gram-negative bacteria with the potential structural diversity to mediate specific adherence. Probably functions as an adhesin.
Teichoic acids and lipoteichoic acids (LTA	Cell wall components of gram-positive bacteria that may be involved in non specific adherence.

further indicated must be able to survive in the small moist droplets produced during sneezing and coughing while pathogens which enter through venereal routes survive best in the warm moist environment of the urogenital mucosa. Microbes entering host through the skin generally survive in a wide range of environments including salivary and alimentary tract of anthropod vectors, mouths of larger animals, soil and water. Characteristically, however, most such pathogens when they land directly on the skin do not survive the harsh environment of this site due to its characteristic low pH and the presence there of antimicrobial factors and fatty acids. Once damaged as in the case of cuts, burns or animal bites, however, the skin can be a major portal of entry and growth for pathogens.

- **Microbial attachment to host tissue, colonisation and growth**

The first stage of microbial infection is colonisation (Todar, 2009:2). After gaining entry into host, microbes anchor themselves to tissue cells through specific ligands or adhesins comprising a wide range of microbial surface structures which may include pili or fimbrae, flagella or various macromolecules notably lipopolyscaccharides and the proteins invasin and haemagglutinins (Todar, 2009:2; Pier, 2005:701; Sudhakar & Subramani, 2005:1). These microbial surface structures, serving generally as pathogen virulence factors, bind and anchor microbes to host tissue receptors or elicit host responses critical to the pathogenic process (Elliot *et al.*, 2004: 6). Some microbes adsorb host proteins onto their surface and utilise natural host receptors for microbial binding and entry into target cell (Todar, 2009:2). Examples of means of microbial attachment to host tissues as indicated by Pier (2005:701) and Todar (2009:3) include the use of pili by most gram-negative bacteria in anchoring to host target cells through such receptors as membrane cofactor protein, CD46, on mucosal epithelial cells by *Neisseria* spp; ceramides, mannose residues or digalactose residues on globosides of the human P blood group by *E. coli*; and Asialo-GMI by *Pseudomonas aeruginosa* or cystic fibrosis transmembrane conductance regulator (TCR) through the pathogen's expression of characteristic lipopolysaccharides that bind to these TCRs. *Yersenia* spp use invasin protein to attach to β_1 integrin receptors while *Legionela pneumophila* and *Mycobacteria tuberculosis* respectively use adsorbed host protein C3bi to anchor to host receptor CR3. Staphylococci and streptococci as further indicated by Pier (2005:701) develop proteins that serve as virulence factors binding to human extracellular proteins like fibrin, fibronectin, laminin, and collagen and making them to adhere to host tissues.

By forming a surface polysaccharide composed of N-acetyl glucosamine and using this to effect their binding to prosthetic devices, coagulase-negative staphylococci and *Staphylococcus aureus* readily colonise these devices to cause infections.

Colonisation of bacterium follows its entry into host. It involves the pathogen establishing itself and growing in its new habitat under local conditions of temperature, pH, nutrient availability and presence of indigenous microbial flora against which it has to compete for survival (Inglis, 2003:19). For it to grow, the pathogen must acquire specific nutrients or synthesise them from precursors in the host tissues. Koczura and Kaznowski (2003:197) cited iron as an example of a required nutrient for bacterial growth and replication and the establishment and progression of bacterial infections. Linking the mechanism of the microbe's acquisition of iron to its virulence, the authors explained that in the host organism, iron is largely unavailable due to the presence of iron-binding glycoproteins such as transferrin and lactoferrin. To grow and multiply under these conditions bacteria require a high affinity iron acquisition system capable of competing with the host iron-binding proteins (Koczura & Kaznowski, 2003:197). They possess, further to the authors' explanation, a system that uses siderophores which are low molecular weight chelators that specifically bind iron outside the cell and are subsequently taken up through receptors in the cell membrane. Examples of such siderophores include aerobactins and enterobactins identified in *Klebsiella pneumoniae* and yersiniabactin described in *Yersinia* spp (Koczura & Kaznowski, 2003:197; Carniel, 2001:561). The presence of siderophores according to Koczura and Kaznowski (2003:197) contributes to the virulence of a wide variety of bacterial pathogens which according to Carniel (2001:561) include also *E. coli*, *Citrobacter* and *Salmonella*. Yersiniabactin for example is encoded by genes clustered in a pathogenicity island named "high-pathogenicity island" and the presence of this so-called "high-pathogenicity island" correlates with the virulence of *Yersinia* spp.

Explaining why pathogens become associated with certain anatomical sites in causing their infections, Pier (2005:702) indicated that since pathogens have varying nutrient requirements as well as local conditions of temperature, pH and oxygen availability for their growth it follows that only pathogens whose growth needs are met in a given tissue they colonise will thrive and cause disease in the host. Many infectious processes according to them, for example, are usually confined to epithelial surfaces - influenza to

respiratory mucosa, gonorrhoea to urogenital epithelium, shigellosis to gastrointestinal epithelium - and one important reason to explain this specificity is the ability of these pathogens to obtain from these environments the nutrients optimum for the local conditions they need for growth.

- **Avoidance of innate host defence mechanisms**

To be able to cause disease in the host, a successfully colonised and growing pathogen must be able to overcome or avoid innate host defence systems that tend to prevent encounters of the pathogen and host from developing into diseases in the host.

Examples of such host defence systems as documented by Inglis (2003:55) and Pier, (2005:702) include the following:

- Restriction of growth of microorganisms on normal skin by a combination of factors such as dryness, high salt concentration, presence on the human skin of fatty acids and other antimicrobial substances toxic to pathogens settling on it, shedding of skin squames. Generally and according to the author, microbial penetration of skin is prevented by the integrity of the epidermis, particularly the stratum corneum and it is probable that skin and soft tissue infections cannot take place without a break in the epidermis, even if only on microscopic scale. Pathogens such as staphylococci that can tolerate the harsh conditions of the skin only can infect it and cause disease in the human hosts.
- The covering of mucosal surfaces by a barrier composed of a thick mucus layer that entraps microbes and facilitates their transport out of the body through processes of mucociliary clearance, coughing and urination.
- The presence in mucous secretions, saliva and tears of antibacterial factors such as lysozymes or antiviral factors like interferon.
- The presence of the complement system in the serum, which when activated leads to the production of a number of products that activate the immune system bacterial invasion (Nicklin *et al.*, 2002:168). Complement is a set of proteins circulating in the blood stream which, on activation by the presence of microbes or antibody-antigen complexes attract phagocytes, enhance phagocytic ability and form a membrane-attack complex which can kill gram-negative bacteria (Nicklin *et al.*, 2002:166).
- Acidity of gastric content which adversely affect the survival of most ingested pathogens.

- The presence on many mucosal surfaces, particularly the nasopharynx, the vaginal tract and the gastrointestinal tract of resident flora of commensal microbes that interfere with pathogen colonisation and infection of host.
- Phagocytic and inflammatory responses as well as host genetic factors that determine the degree to which a pathogen can survive and grow.

Among the above indicated host defence mechanisms phagocytosis of microbes is a major innate host defence that limits the growth and spread of pathogens. Ingestion of microbes by both tissue-fixed macrophages and migrating phagocytes to a large extent is responsible for the limited ability of most microbial agents to cause disease. Bacterial pathogens are ingested principally by polymorphonuclear neutrophils (PMNs) and for a pathogen to successfully infect a host and cause disease it must avoid being cleared by phagocytes (Pier, 2005:703).

In spite of presence of these host defence mechanisms as described, some pathogenic bacteria are inherently able to resist the bactericidal components of host tissues, particularly avoiding phagocytic clearance and to survive and cause infections or disease in the host (Todar 2009:5).
Some strategies employed by pathogens to escape phagocytic clearance include the following:

- Elaboration of large molecular weight surface polysaccharide antigens in the form of a capsule that coats the cell surface to prevent its ingestion by the phagocytes (Todar, 2009:5).

- Production of factors that are either toxic to the phagocytes or interfere with the chemotactic and ingestion function of phagocytes. Some pathogens for example elicit microbial proteins like haemolysins and leukocidins that kill phagocytes attempting to ingest them (Elliot *et al.*, 2004:27). Typically for example staphylococci haemolysins inhibit macrophage chemotaxis and kill these phagocytes. Coagulase produced by *Staphyloccocus aureus* coagulates plasma and causes fibrin deposition which interferes with phagocytosis and increases the ability of the organism to invade tissue. Streptolysin O produced by *StreptococcuS. pyogenes* binds to cholesterol in phagocyte membranes and initiates a process of internal degranulation with the release of granule sequestered toxic components into the

phagocytes cytoplasm (Elliot *et al.*, 2004:27; Todar, 2009:5). Antiphagocytic substances on the bacterial surface polysaccharide capsule of *Haemophilus influenzae*, *Treponema pallidum* and *Klebsiella pneumoniae, surface slime (polysaccharide) produced by Pseudomonas aeruginosa,* O antigen associated with lipopolysaccharide of *E. coli* (Todar, 2009:5), K antigen of *E. coli* or the analogous Vi antigens of salmonella typhi (Todar, 2009:5).

- Development of mechanisms by the pathogen that allows it to survive in the phagocyte after being ingested. *M. tubercolulosis*, *Salmonella typhi* and the protozoa *Toxoplasma gondii* survive inside macrophages by inhibiting the fusion of the phagocytic vacuole containing the ingested microbe with the lysosomal granules containing antimicrobial substances supposed to kill them if fusion takes place (Pier, 2005: 703; Todar, 2009:5).

Todar (2009: 5) indicated further as examples of pathogens' avoidance of innate host defence mechanisms by mentioning:

- the protection of *Bacillus anthracis by* the poly-D-glutamate capsule that protects the organisms against cell lysis by cationic proteins in sera or in phagocytes and

- the avoidance of penetration of hydrophobic substances into gram-negative bacteria by the presence of an outer membrane that formed formidable barrier penetration of such substances.

- **Tissue invasion and tissue tropism**

Following successful colonisation at a site of infection, bacteria pathogens may invade deeper layers of mucosal tissue in a process referred to as microbial tissue invasion. The process is of two types, namely, extracellular and intracellular processes of invasion (Wilson *et al.*, 2002:219). Extracellular invasion according to the authors, occurs when a microbe breaks down the barriers of a tissue to disseminate in the host while remaining outside the host cells. Intracellular invasion on the other hand occurs when a microbe actually penetrates the cells of a host tissue and survives in this environment. A number of gram-negative, gram-positive and mycobacterial pathogens have been shown to have the ability to enter host cells and use their ability to enter and

survive within host cells as a means of spreading to other tissues (Wilson *et al.*, 2002:219). Mechanisms by which tissue invasion takes place differ from one bacterial type to another and may even be poorly understood in the case of certain pathogens. Generally, however, the process occurs through the organism's uptake by epithelial cells, its traversal of epithelial cell junctions or penetration through denuded epithelial surfaces (Pier, 2005:704). It may involve the use of microbial membrane proteins or enzymes elaborated by the invading microbe. Some examples of mechanisms of bacterial tissue invasion as cited by Pier (2005:704), Elliot *et al.* (2004:27) and (Todar 2009:4) include the following:

- The elaboration of variety of extracellular enzymes such as hyaluronidase, lipases, proteinases, haemolysins by certain bacteria for example staphylococci and streptococci that are probably responsible for breaking down cellular matrix structures to allow bacteria access to deeper tissues and blood. These enzymes, or any such substance produced by bacteria extracellularly to act against the host by breaking down the primary or secondary defences of the body are referred to as invasins (Todar, 2009:4). Descriptively they are also termed spreading factors because of their abilities to affect the physical properties of tissue matrices and intercellular spaces to promote the spread of the pathogen (Todar, 2009:4). They respectively dissolve hyaline, solubilise lipids, degrade proteins and lyse erythrocytes and damage platelets. *Shigella* and invasive *E. coli* are known *to* use outer membrane proteins in epithelial cell invasion (Pier, 2005:704; Elliot *et al.,* 2004:27).
- Use of invasin protein by *Yersinia enterolitica* in invading the mucosa (Pier, 2005:704).
- Transportation of some bacteria for example *Brucella* by phagocytes that ingest but do not kill them from a mucosal site to a distant site (Pier, 2005:704).

Other invasins employed by pathogens to invade tissues as mentioned by Todar (2009:4) include the production of the following:

- Collagenase by *Clostridium histolyticum* and *Clostridium perfringens* to break down collagen the framework of muscles, and facilitate the development gas gangrene due to these organisms.
- Neuraminidase by intestinal pathogens e.g. *Vibrio cholerae* and *Shigella dysenteriae* to degrade neuraminic or sialic acid, an intercellular cement of the

epithelial cells of the intestinal mucosa to facilitate their invasion of these intestinal tissues.

- Streptokinase and staphylokinase being produced by streptococci and staphylococci respectively. These kinases activate inactive plasminogen to active plasmin which digests fibrin and prevents blood clotting. Absence of blood clots promotes rapid diffusion of the infectious bacteria to other areas of the tissue.
- Bacterial toxins with adenylate cyclase activity. These are thought to have immediate effect on host cells that may promote bacterial invasion. According to Todar (2009:4) one component of the anthrax toxin, oedema factor, is an adenylyl cyclase that acts on nearby cells to cause increased levels of cyclic adenosine monophosphate (cAMP) and the destruction of cell permeability. Further to the authors explanation one such toxin of *Bortella pertussis*, the agent of whooping cough, has a similar effect. The agents by the author's explanation may contribute to invasion through their effects on macrophages or lymphocytes in the vicinity as they play their role to control the infection. The use of adenosine triphosphate (ATP) in the formation of cAMP, is thought to deplete phagocytes of the energy source they need in ingestion of the invading pathogens (Todar, 2009:4).

At a stage of its spread *Staphylococcus aureus* at a point produces coagulase enzyme that converts fibrinogen to fibrin which causes clotting. This is not associated with non pathogenic *S. epidermidis*. It is thought that cell bound coagulase could provide an antigenic disguise if it clotted fibrin at cell surface. On the other hand a staphylococcal lesion encased in fibrin e.g. boil or pimple, could make the bacterial cells resistant to phagocytes or tissue bactericides or even drug which might be unable to diffuse to their bacterial targets (Todar, 2009:4).

Some pathogens have obligate intracellular lifecycle which, according to Wilson *et al.* (2002:219), absolutely requires growing mammalian cells. Examples of such pathogens by the authors' indication include *Chlamydia* spp, *Rickettsia* spp, and *Mycobacterium leprae*. In recent years genes that allow pathogens to invade host non-phagocytic cells have been identified and is considered a major advance in understanding bacterial pathogenesis by intracellular mechanisms (Wilson *et al.,* 2002:219). These invasion genes present in different pathogens and encode an evolutionarily related type III protein secretion pathway that serves to inject signalling proteins from the microbe into the cell.

The injected proteins tend to activate host cell signalling pathways that cause internalisation of the microbe. This entry mechanism are well characterised in *Salmonella* spp and *Shigella* spp (Wilson *et al.,* 2002:219).

- **Microbial damage of host tissue and causation of disease**

Disease resulting from bacterial infections may emanate from microbial tissue invasion or destruction, microbial toxin elaboration and/or host response to the infection (Pier, 2005:705). Growth of bacteria in tissue can compromise tissue function and cause disease. Pneumococcal pneumonia is attributable mainly to the growth of *Streptococcus pneumoniae* and the formation by the pathogens of capsular polysaccharide in the lung which largely is attributable to the attendant inflammatory host responses associated with the disease (Wilson *e al.,* 2002:219). Similarly meningitis producing bacteria such as *Neisseria meningitidis*, *H. influenzae*, *E. coli* K1, and group B streptococci appear to produce this disease by their ability to gain access to the meninges, multiply in them and provoke cytokine production leading to inflammation and tissue damage (Stevens *et al.*, 2005: 849)

According to Inglis (2003:20), toxin production is the best characterised molecular mechanisms of pathogenesis for most bacteria. They are usually either proteins released by the organism (exotoxins) (Wilson *et al.,* 2002:218; Todar, 2009:7) or a lipopolysaccharide complex (endotoxins) located in the cell wall and which are liberated during cell wall growth or lysis (Wilson *et al.*, 2002:217; Inglis, 2003:20; Todar, 2009:7). Many exotoxins have two principal subunits, a binding or B subunit and an active or A subunit which respectively determine tissue specificity for toxin binding and causation of tissue damage and pathogen penetration of cell membranes (Todar, 2009:9; Pier, 2005:705).

As a point of note, Todar (2009:7) mentioned that bacterial toxins, particularly those acting as enzymes are highly specific in the types of host substrate they utilise in their modes of action in causing disease. The substrate may be a component of tissue cells, organs, or body tissue and usually, the site of damage caused by the toxin will be indicative of the location of the substrate for that toxin. Terms such as enterotoxin, neurotoxin, leukocidin or haemolysin are for example sometimes used to indicate the target site of some well defined protein toxins. Since such protein toxins are associated

with particular class or classes of pathogens that elaborate them, diseases caused by them at the specifically indicated sites would also provide a clue to the pathogens causing them. This, in addition to the explanation of Pier (2005:702) regarding pathogens being provided by nutrients and favourable conditions for growth at certain anatomical body sites, provides further reasons that explain why certain pathogens become associated with infections at specific sites of the body.

Bacterial pathogens causing disease through toxin production as exemplified by Pier (2005:705) include:

- *Corynebacterium diphtheriae*, *Clostridium butulinum* and *Clostridium tetani* respectively produce diphtheria, botulinum, and tetanus toxins that are responsible for diseases associated with their infections.
- *E. coli*, *Salmonella*, *Shigella*, *Staphylococcus* and *Vibrio cholerae* produce enterotoxins that are responsible for the diarrhoeal diseases caused by these organisms. Vibrio cholerae causes the most severe diarrhoeal disease because of the action of a toxin that binds to the receptors at the ganglion on the intestinal mucosa to stimulate the production of cyclic adenosine monophosphate (cAMP) to block sodium and water resorption from the small intestine (Inglis, 2003: 250).
- *Pseudomonas aeruginosa* and *Bordetella* elaborate various toxins including toxic shock syndrome toxin 1 (TSST-1), erythrogenic toxin, exotoxins A, S, and U and pertussis toxin, that cause or contribute to diseases associated with them (Pier, 2005:705).

Various bacterial toxins as stated in Pier (2005:705) produce disease by different mechanisms of action. According to the author, a number of toxins, for example cholera, diphtheria, pertusis, *E. coli* heat labile and *P. aeruginosa* exotoxins, have adenosine diphosphate (ADP)-ribosyltransferase activity that is able to enzymatically catalyse the transfer of ADP-ribosyl subunit of nicotinamide adenine diphosphate (NADP) to target proteins and inactivate them. This results in an alteration of cellular homeostasis and may clinically demonstrate as the disease associated with the infection in question. Some other toxins for example staphylococcal enterotoxins, TSST-1 and streptococcal pyogenic exotoxins behave like superantigens. This group of antigens by indications of Pier (2005:705) and Nicklin *et al.* (2002:179) stimulate certain T-helper cells to proliferate. The proliferation process according to Pier (2005:705) partially stimulates

antigen-presenting cells to produce interleukin-1 (IL-1) and tumour necrosis factor α (TNF-α) which are implicated in many of the clinical features of diseases like toxic shock syndrome and scarlet fever .

Endotoxins (lipopolysaccharides (LPS)) are important in pathogenesis of gram-negative septic shock and many other clinical manifestations of gram-negative bacterial infections like fever, muscle proteolysis and uncontrolled intravascular coagulation (Elliot *et al.*, 2004:157; Pier, 2005:705; Nicklin *et al.*, 2002:179). Unlike exotoxins, endotoxins of prokaryotic cell wall are distinct structural components that are not released appreciably into the extracellular medium until cell death and lysis of the bacteria occur (Wilson *et al.*, 2002:217). LPS has a molecular portion referred to as lipid A portion (Nicklin *et al.*, 2002:179, Wilson *et al.*, 2002:217). This molecular portion of the endotoxin binds with membrane proteins CD14 to induce signal transduction via Toll-like receptors (TLRs) to cause the release of numerous pro-inflammatory cytokines. These have potent biologic activities, further to the authors' indications that include the activation of complement and coagulation cascades in the host to cause many of the indicated clinical manifestations of gram-negative bacteria infections. Cytokines according to Pier (2005:705) exhibit potent hypothermic activity on the hypothalamus, and also increase vascular permeability that ultimately result in shock. They also activate clotting and fibrinolytic cascades resulting in haemorrhage and thrombosis (Elliot *et al.*, 2004:157).

Bacteria infections can in summary be seen as promoting series of complex host inflammatory responses that involve activation of complement, kinin and coagulation pathways to cause pathological changes demonstrating in the host as observed disease in the host associated with the infection. These host responses to infections as noted by Pier (2005:706), are critical for interruption and resolution of the infectious process but they are at the same time also responsible for the many signs and symptoms of infectious diseases. To this effect and further to the author's indications, it can be said that the outcome of infection is a balance between an effective host response to eliminate a pathogen and an excessive inflammatory process that fails to eliminate the infection (Pier, 2005:706). Generally, the nature of host response elicited by the pathogen determines the pathology of a particular infection.

In the case of gram-negative bacteria mostly, the activation of the above indicated pathways responsible for the infection occur as a result of interactions of microbial cell wall components (endotoxins) with receptors on host cells to initiate cellular signalling pathways. Unlike endotoxins, exotoxins are released into the medium by growing bacteria and on account of their water solubility they can act at sites distant from original sites of infection (Nicklin *et al.*, 2002:179). The initiation of cellular signalling pathways as indicated results in host cell production of pharmacologically active substances, principally cytokines (e.g. IL-1 and TNF-α) inflammatory proteins, products of complement activation, mediators derived from arachidonic acid metabolites (leukotrienes) and cellular degranulation (histamine) that contribute to the pathogenesis and severity of disease (Pier, 2005:705). Abscess formation is associated with a number of bacterial infections. It is provoked by a number of pathogens, particularly anaerobic bacteria, staphylococci and streptococci because of the presence in them of zwitterionic surface polysaccharides such as the capsular polysaccharide of *Bacteroides fragilis* (Pier, 2005:706).

2.1.4 Gram-positive bacterial pathogens: Pathogenesis, antibiotic susceptibilities associated infections and recommended treatments.

General mechanisms of bacterial pathogenesis were reviewed in previous paragraphs. This section reviews the pathogenesis, antibiotic susceptibilities, associated infections and recommended treatments of infections caused by gram-positive bacterial pathogens. Pathogens that appear to be regularly isolated in the microbiology laboratories of study site hospitals and also atypical pathogens that may be implicated in diagnosed infections but are not regularly isolated due to problems associated with their isolation and culturing particularly have been targeted for this review.

2.1.4.1 *Streptococcus* and *Enterococcus* spp

Streptococci are gram-positive cocci often seen growing in pairs or chains (Inglis, 2003:244; Wessels, 2005:823). They are non-sporing facultative aerobes which may occasionally be capsulate (Wessels, 2005:823; Elliot *et al.*, 2004:30). Enterococci, have similar characteristics as streptococci and were formerly classified in the genus *Streptococcus.* They differ from the latter in their ability to grow on bile salt containing media (Elliot *et al.*, 2004:30).

- **Classification of Streptococci**

Streptococci vary in their exhibition of properties they have in common as a genus and are hence classified into different subgroups based on variations in their group properties (Elliot *et al.*, 2004:30). Some members of the genus according to the authors, characteristically cause haemolysis while some do not and typical streptococcus can be described as haemolytic or non-haemolytic. Among those causing haemolysis as they indicated, some have the ability to form green pigments from the degradation products of haemolysed erythrocytes and hence form greenish zones around their colonies on blood growth agar. These are classified as **α-haemolytic streptococci** in contrast to **β-haemolytic streptococci** which also haemolyse blood but form clear zones around their colonies (Wessels 2005:823). Streptococci that do not haemolyse erythrocytes are classified as **non-haemolytic streptococci**. Apart from their classifications based on their abilities to haemolyse red blood cells, some streptococci also have carbohydrate antigens in their cell envelops that give different reactions to antibodies in agglutination tests. This property of the pathogens is also used as a basis for their classification in a system known as the Lancefield system of classification. With this system streptococci are classified into subgroups designated by letters of the alphabet. Commonly we have streptococci of Lancefield Groups A, B, C, D and G with Group D streptococci being reclassified as Enterococcus (Elliot *et al.*, 2004: 30,31) .

The various groupings of streptococci of pathologic importance, their definitions, representative species and epidemiology, are provided in Table 2.2.

Table 2.2: Group definitions and epidemiology of streptococci. (Compiled from information gathered from Musher, 2005:806 & 807; Elliot *et al.*, 2004: 30 -37; Wessels, 2005:823 & 824)

Haemolytic pattern	Lancefield Group	Representative species	Epidemiology
α-haemolytic streptococci	Non groupable	*S. pneumoniae* also referred to as Pneumococcus	*S. pneumoniae* is a normal inhabitant of the upper respiratory tract. It colonises the nasopharynx of 5-10% of adults and up to 20- 40% of children. It spreads by droplet transmission from one individual to another. Incidence of bacteraemia pneumococcal infection is high in infants up to 2 yrs of age, low among teenagers and begins to increase from age 55
	Non groupable	Viridans streptococci: *S. sanguis, S. mitis*	Viridans streptococci are part of normal oral flora. Also commensals of upper respiratory and gastrointestinal tracts. They are however important as agents of subacute bacterial endocarditis
β-haemolytic streptococci	A	*S. pyogenes*	Commensals of upper respiratory tract of about 5% and 10% of adults and children respectively. Accounts for up to 40% of all cases of bacterial pharyngitis in children. Rare among children under the age of 3. Transmission is via droplet spread
	B	*S. agalactiae*	Forms part of perineal flora in about 30-40% of individuals
	C	*S. equisimilis*	Common cause of infections in domesticated animals particularly horse and cattle. Infections in humans very often acquired through contact with animals or through consumption of pasteurised milk.
	G	*S. canis*	As for Group C streptococci
Non-haemolytic streptococci	D	Enterococci: *E. faecalis, E faecium*	Normal flora of the gastrointestinal tract. Can grow in the presence of bile
		Non enterococci: S bovis	
		Anaerobic streptococci: *Peptococcus* and *Peptostreptococcus* spp (*P. magnus, P micros, P. anaerobius*)	Commensals of bowel and vagina
Variable	Non groupable	Intermedius, mileri or anginosus group: Also considered viridans streptococci. *S. intermedius, S. anginosus and S. constellatus*	Commensals of oropharyngeal flora

- **Mechanisms of streptococcal pathogenesis**

Streptococci vary in their degrees of virulence and mechanisms of disease causation. The pathogenic mechanisms and virulence factors of the major medically important members of the genus are summarised in the subsections that follow.

° **Mechanisms of *Streptococcus pneumoniae* (Pneumococcus) pathogenesis**

The pathogen attaches to human nasopharyngeal epithelial cell receptors using bacterial surface adhensins such as pneumococcal surface antigen A or choline binding proteins Musher, 2005:806). The bacteria colonised as such spread from the nasopharynx into nearby anatomical areas e.g. the eustachian tube or nasal sinuses to cause infection if its clearance is hindered, for example, by mucosal oedema due to allergy or viral infection. Pneumonia ensues in situations when the organism is inhaled into the lungs and is not cleared as, for example, in cases of viral infection or presence of toxic substances like cigarette smoke which may cause increase mucus production and/or damage to ciliary activity.

Except for strains that cause conjunctivitis, nearly all clinical isolates of *S. pneumoniae* has a polysaccharide capsule which promotes the virulence of the organism by preventing its ingestion by phagocytic cells (Inglis, 2003:245; Wilson *et al.*, 2002:216). At its initial site of infection the organism, through its cell wall components (teichoic acid, C substance, peptidoglycan), as indicated by Musher (2005:807), initiates inflammatory processes by activating complements and stimulating the production of cytokines. These include, for example, cytokine 5a (C5a), which attracts to the site of infection PMN leukocytes and pro-inflammatory substances, notably IL-1β and TNF α. These activate a cascade of inflammatory mediators that further promote PMN migration to the site of infection. In the presence of their polysaccharide capsules however, the organisms resist ingestion by the polymorphonuclear leucocytes and continue to replicate to form a large bacterial inoculum that disseminates from the site of infection for example in the lungs to infect other body tissues like the meninges, joints, bones and peritoneal cavity .

° **Mechanisms of Group A (β-haemolytic) streptococci (*S. pyogenes*) pathogenesis**

S. pyogenes has a major surface protein, M protein that enables it to resist phagocytosis by a mechanism which in part involves the organism's attachment to host proteins e.g.

fibrinogen and interfering with complement activation and deposition of opsonic fragments on the bacterial cell (Eliot *et al.*, 2004:32; Wessels, 2005:824). Further to the authors' explanations of ways and means by which the pathogens cause disease they indicated that *S. pyogenes* also elaborates a polysaccharide capsule composed of hyaluronic acid that both helps to protect it from phagocytic ingestion and killing. They colonise the pharynx according to Wessels (2005:824) by binding to CD44, a hyaluronic acid binding protein expressed on human pharyngeal epithelial cells. Additionally, the pathogens also produce a large number of extracellular toxins and enzymes that account for their ability to invade tissues and their production of systemic toxicity. These include, for example, pyrogenic exotoxins A, B, and C previously known as erythrogenic toxins which are responsible for the rash in scarlet fever (Elliot *et al.*, 2004: 32). Others include streptolysins S and O, toxins that damage cell membranes, streptokinase, DNases and proteases (Wessels, 2005:824;).

- **Mechanisms of other streptococci pathogenesis (*S. agalactiae*)**

Apart from its capsular polysaccharide being experimentally found to be important in its virulence (Wessels, 2005:823), the virulence factors for *S. agalactiae* (Group B streptococci) are not well defined (Elliot *et al.*, 2004:33).

Viridans streptococci possess few virulence factors. The organisms attach to tooth enamel and gums and form colonies by the use of various carbohydrates. Their ability to produce acid, particularly *S. mutants* has been implicated in the development of dental caries (Elliot *et al.,* 2004:34).

- **Streptococcal associated infections**

- ***Streptococcus pneumoniae* (Pneumococcus) associated infections**

S. pneumoniae is associated with infections of various anatomical sites including the middle ear (otitis media) and the respiratory tract by direct spread from the nasopharyngeal site of colonisation, and the central nervous system (CNS), heart valves, bone joints and peritoneal cavity by haematogenous spread (Musher, 2005:808; Elliot *et al.*, 2004:34). Specifically the pathogen is associated with the following infections:

- **Otitis media and sinusitis**: *S. pneumoniae* is second to *Haemophilus influenzae* as a causative agent for otitis media and sinusitis (Musher, 2005:808; Elliot *et al.*, 2004: 34). Allergy or prior infection by a respiratory virus, by causing congestion of the eustachian tubes or the paranasal sinuses is thought to significantly contribute to the development of these infections.
- **Pneumonia**: *S. pneumoniae* is the most common cause of lower respiratory tract infections (Elliot *et al.,* 2004:34) and is the undisputed major pathogenic bacterium associated with community acquired pneumonia (Musher, 2005: 808). Distinctive signs and symptoms of bacterial pneumonia according to Musher (2005: 808): are cough and sputum production due to bacteria proliferation and inflammatory response, fever and radiographic detection of an infiltrate. Characteristically, *S. pneumoniae* associated pneumonia according to the author is most common in extremes of age and the majority of adults have underlying disease or factors that reduce normal host resistance predisposing them to the infection. These may include such diseases or factors as prior viral illness, alcoholism, malnutrition, chronic obstructive airways disease, diabetes mellitus, cigarette smoking, HIV infection, liver cirrhosis, anaemia, renal insufficiency, coronary disease or prior hospitalisation of any kind. Pneumococcal infection of the lung in the community is often associated with an extensive list of many other organisms (Musher, 2005:809). These may include *Haemophilus influenzae or Moraxella catarrhalis* in persons with little to expose them to the infection other than acute or chronic inflammation of the airways; *S. aureus* in persons who take glucocorticoids; *StreptococcuS. pyogenes*; *Neisseria meningitidis*, and anaerobic species in persons who have seizures or who have aspirated oropharyngeal contents for some other reason; *Legionella*; gram-negative bacteria in persons with severely damaged lungs who are taking glucocorticoids; viruses; *Mycoplasma*; *Clamydia pneumoniae*, particularly in older adults; *Pneumocystis carinii*, and *Mycobacterium tuberculosis*. Table 2.3 is a compilation of features of pneumonia caused by different organisms and is intended to serve as a guide in making decisions during antibiotic selection for presumptive treatment of the infections. .

- **Meningitis**: *S. pneumoniae* is an important cause of bacterial meningitis, and is considered the most common cause of the disease in adults particularly in the elderly (Elliot *et al.*, 2004:34; Musher, 2005:810). It infects the meningeal membrane through either homogenous seeding or by extension from infections of the sinuses

Table 2.3: Features of Pneumonia caused by different bacteria

(Compiled from information obtained from Musher, 2005:809; Inglis, 2003:76; Russo, 2005: 882)

Organism	Predisposing factor to infection	Symptoms
Streptococcus pneumoniae	Common in extremes of age. Associated very often in majority of adult patients with underlying diseases and etiologies that include prior viral illness, alcoholism, malnutrition, chronic obstructive airways disease, diabetes mellitus, cigarette smoking, HIV infection, liver cirrhosis, anaemia, renal insufficiency, coronary disease or prior hospitalisation of any kind.	Sudden onset pleuritic pain, fever, rusty sputum, cold sores; or Pneumonia in the chronic bronchitic
Staphylococci aureus	Long term use of glucocorticoids or pneumonia following influenza	
Haemophilus influenzae	Acute or chronic inflammation of the airways i.e. chronic or acute bronchitis	
Klebsiella pneumoniae	Predisposing disease e.g. alcoholism, diabetics; hospitalisation, Mechanical ventilation	Thick viscous purulent red sputum, pneumothorax on X-ray
Moraxella catarrhalis	Associated with pneumonia in older adults, long history of cigarette smoking, underlying chronic obstructive pulmonary disease or lung cancer and malnutrition.	
Mycoplasma pneumoniae	Associated with pneumonia in older adults	Non productive cough, pharyngitis in young adult, ambulant despite positive chest X-ray
Legionella pneumophila	Being a middle aged male, smoking, exposure to air conditioning or hotel shower	Non productive cough, confusion, diarrhoea,
Mycobacterium tuberculosis	Vagrant or alcoholic	Upper lobe consolidation, hilar lymphadenopathy,
Chlamydia pneumoniae	Associated with pneumonia in older persons	
Chlamydia psittaci	Association with birds	

or middle ear. Symptoms of pneumococcal meningitis which include fever, headache, and stiffness or pain in the neck, do not differ from meningitis due to other bacteria (Musher, 2005:810). Like pneumonia, other organisms, notably *H. influenzae* and *N meningitidis* are involved as causative agents of bacterial meningitis. *H. influenzae* principally cause the infection in unvaccinated preschool children < 5 years of age while *S. pneumoniae* and *N. meningitidis* are the main aetiological agents of the disease in older children and adults (Inglis, 2003:130).

- **Other possible pneumococcal infections**

  Possible haematogenous seeding of *S. pneumoniae* at certain sites in the body during frank pneumonia or metastasis of the organism from rather non-apparent foci of infection can result in pneumococcal infections of otherwise sterile body sites (Musher, 2005:810). Such infections, some of which though may be rare, are of common place occurrence in clinical practice. Examples as indicated by the authors include the rare cases of pneumococcal endocarditis and purulent pericarditis; septic arthritis; osteomyelitis often involving the vertebral bones; peritonitis resulting from haematogenous spread, local spread from a perforated viscus or transit through fallopian tubes; and epidural or brain abscess arising as complication of sinusitis or mastoiditis and cellulitis in persons with connective tissue disease or HIV infection. Unencapsulated *S. pneumoniae* is also recognised as a cause of sporadic or epidemic conjunctivitis (Musher, 2005:810). Patients who have had splenectomies or whose spleen is functionally impaired have a reduced capacity to produce IgG (immunoglobulin G) and are particularly susceptible to invasive pneumococcus disease (Elliot *et al.*, 2003:34).

- **Group A streptococci (*S. pyogenes*) associated infections**

S. pyogenes according to Elliot *et al.* (2004:32) and Wessels (2005:824-828), is associated with infections of the upper respiratory tract (URT) (pharyngitis, tonsillitis and otitis media) and skin and soft tissues (cellulitis, necrotising fasciitis, impetigo, erysipelas, wound infections and scarlet fever). It also causes invasive infections notably bacteraemia (septicaemia) and puerperal sepsis. The pathogen also causes toxic shock syndrome through the effects of various exotoxins it produces e.g. pyrogenic exotoxin A with general features of the illness including fever, hypotension, renal impairment, and respiratory distress syndrome (Wessels, 2005: 828).

Streptococcal pharyngitis as Musher (2005: 824) stated is one of the most common bacterial infections in childhood and accounts for 20 – 40% of all cases of exudative pharyngitis in children. Usual symptoms include sore throat, fever, chills, malaise and sometimes abdominal complains and vomiting particularly in children. Severity of symptoms may vary from mild throat discomfort to high fever and severe sore throat associated with intense erythema and swelling of the pharyngeal mucosa and the presence of purulent exudate over the pharyngeal wall and the tonsils. A large number of agents according to the author notably viruses and other bacteria (e.g. *Neisseria gonorrhoea, Mycoplasma pneumoniae, Corynebacterium diphtheria and Arcanobacterium haemolyticum*) can produce the same clinical picture as what is seen in streptococcal pharyngitis. This makes diagnosis of streptococcal pharyngitis unreliable in absence of a throat culture. Streptococcal infection can however be assumed to be the unlikely cause of pharyngitis when signs and symptoms suggestive of viral infection, that is conjunctivitis, coryza, cough, hoarseness or discrete ulcerative lesions of the buccal or pharyngeal mucosa, are present.

- **Scarlet fever** presents usually as streptococcal pharyngitis with rashes that arise from the effects of streptococcal pyrogenic exotoxins A, B, and C (Musher, 2005:825).

- *S. pyogenes* is a primary cause of **impetigo,** a superficial skin infection that starts as individual red papules and evolve quickly into vesicular and then pustular lesions which break down and coalesce to form characteristic honeycomb crusts. Cultures of impeginous lesions also yield *Staphylococcus aureus* in addition to *S. pyogenes* as implicating pathogens (Musher, 2005: 826). Streptococcal **cellulitis** or **erysipelas** is characterised by a bright red appearance of the involved skin which forms a plateau sharply demarcated from the surrounding normal skin. It typically occurs in the lower extremities and malar region of the face (*region of the cheek or cheek bone of face*) with extensions over the bridge of the nose. Other β-haemolytic streptococci, mainly Group C and G, and also *Staphylococcus aureus* are also causative agents of cellulitis (Musher, 2005: 827). *S. pyogenes* is also a major causative agent of **necrotising fasciitis**, an infection of the subcutaneous soft tissues involving the superficial and deep fascia. It may also involve other bacteria like *S. aureus*, anaerobic bacteria such as *Bacteroides fragilis* and anaerobic streptococci (Inglis, 2003:62). The pathogen also occasionally causes

myositis, an infection of the skeletal muscles characterised with the formation of abscesses within the skeletal muscle. The infection is however most commonly associated with *S. aureus* as its major causative agent. *S. pyogenes* is among the few bacterial pathogens that typically produce signs of **wound infections** and surrounding cellulitis within 24 hours of surgery. Such wound infections are associated with a thin exudate and may spread rapidly either as cellulitis or deeper tissue infections (Musher, 2005: 827).

- The pathogens also occasionally cause **pneumonia**. Streptococcal pneumonia characteristically demonstrates pleuritic chest pain, fever, chills and dyspnoea as symptoms and may in about 50% of patients be accompanied by pleural effusion (Musher, 2005: 827).
- Group A streptococcal **bacteraemia** occurs frequently with necrotising fasciitis and occasionally with cellulitis or pneumonia. The organisms are also implicated in infectious complications of child birth like **puerperal sepsis** which currently however is associated more with Group B rather than with Group A streptococci (Musher, 2005: 828).

° **Group B streptococci (*S. agalactiae*) associated infections**

Group B streptococci (*S. agalactiae*) are a frequent cause of **peripartum fever**. The organisms easily colonise infants delivered vaginally by mothers who are vaginal or rectal carriers of the pathogens. They are major causes of **neonatal sepsis and meningitis.** In neonatal sepsis the neonate patients may typically demonstrate respiratory distress, lethargy, and hypotension as symptoms. Meningitis as a neonatal infection caused by Group B streptococci manifests most commonly in infants with a mean age of 3 – 4 weeks. Major symptoms are fever, lethargy or irritability, poor feeding and seizures (Musher, 2005: 829).

• **Groups C and G streptococci associated infections**

Groups C and G streptococci cause infections similar those of Group A. These include pharyngitis, cellulitis and soft tissue infections, pneumonia, bacteraemia, endocarditis and septic arthritis (Wessels, 2005:828)

- **Group D (non-haemolytic) streptococci (Enterococci and non-enterococcal streptococci) associated infections**

Enterococcus faecalis and *Enterococcus faecium* are the most significant pathogens of the enterococci. Their principal habitat is the gastrointestinal tract (Elliot *et al.*, 2004:36, Inglis, 2003:245). The notable non-enterococcal member of the group causing human infections is *S. bovis* and is a known causative agent of **endocarditis** (Wessels, 2005:831). *E. faecalis* and *E. faecium* are more associated with infections in patients who are elderly or debilitated, patients in whom the balance of normal flora has been altered by antibiotic treatment or patients in whom the mucosal or epithelial barrier has been disrupted for example by catheterisation or instrumentation of any kind (Wessels, 2005:830). In these patients by the author's indications, they may be causative agents for **urinary tract infections** and **nosocomial bacteraemia**. They are also frequent causes of **endocarditis, liver abscesses, infectious complications of biliary surgery**, and also form part of polymicrobial infections in the abdomen (intraabdominal abscess, infections of abdominal surgical wounds) and **diabetic foot ulcers** (Musher, 2005: 830).

- ***Viridans Streptococci* associated infections**

Viridans streptococci (e.g. *S. salivarius, S. mitis, S. sanguis and S. mutans*) are important causes of **bacterial endocarditis**. Some members of the group contribute to the development of **dental caries**. They may also cause **bacteraemia** in patients with certain risk factors, notably chemotherapy with high dose cytosine arabinoside, prior treatment with co-trimoxazole or a fluoroquinolone, treatment with antacids or H_2 - histamine receptor antagonists and mucositis. The *S. mileri* group of streptococci (*S. mileri, S. anginosus* and *S. constellatus*) also considered as viridans streptococci, produces **suppurative infections** particularly abscesses of the brain and the abdominal viscera (Musher, 2005: 831).

- **Anaerobic streptococci (Peptostreptococci) associated infections**

The major anaerobic gram-positive cocci, peptostreptococcus and peptococcus spp are found in the enteric and vaginal flora (Inglis, 2003:245; Wessels, 2005:831). Peptostreptococcus are the major species of the genus involved in infections and are exemplified by *Peptoetreptococcus magnus, P. micros, P. asacharolyticus, P. anaerobius* and *P. prevotii* (Kasper, 2005: 940). They are obligate anaerobes and exist

together with other anaerobic bacteria, principally anaerobic gram-negative bacilli (*Bacteroides*, *Fusobacterium*, *Prevotella* and *Porphyromonas*) and anaerobic gram-positive bacilli (*Clostridium* and *Propionibacterium* spp), and are normal commensals of mucosal surfaces of mouth, lower gastrointestinal and female genital tract. They cause mixed infections with these other anaerobic organisms when a mucosal barrier of the skin is compromised by surgery, trauma, tumour and ischemia or necrosis (Kasper, 2005: 940). Together with these other anaerobic pathogens as noted by Kasper, 2005: 943) they are implicated in a number of infections that include **central nervous system infections,** notably brain abscesses; **aspiration pneumonitis** (Kasper, 2005: 942); **pelvic infections** (e.g. pelvic abscess, septic abortion, endometritis); possibly **bacterial vaginosis**; **necrotizing fasciitis** and **synergistic gangrene and other skin and soft tissue infections** at sites prone to contamination with faeces or upper airways secretions e.g. wound associated with intestinal surgery; decubitus ulcers or human bites (Kasper, 2005: 943). They are also noted with bone and joint infections particularly infections involving the skull, mastoid and prosthetic implants in bones (Kasper, 2005: 944).

For presumptive diagnosis of what could possibly be an anaerobic infection, Kasper (2005:944) noted the following as points physicians must consider as they make such initial diagnoses. These include the following:

- Conditions favouring the propagation of anaerobic bacteria particularly lowered oxidation-reduction potential must exist to favour the growth and pathogenesis of this group of bacteria. These conditions, according to Kasper (2005:944) exist at sites of trauma, tissue destruction, compromised vascular supply and complications of pre-existing infection, which produce necrosis.
- Generally anaerobic organisms tend to be found in abscess cavities or in necrotic tissue.
- The failure of abscess to yield organisms on routine culture is a clue that the abscess is likely to contain anaerobic bacteria and the presence of these bacteria as aetiologic agents of the pus production can be revealed when Grams stain is performed.
- Malodorous abscess suggests anaerobic infection.
- Abscesses in organs or deeper body tissues, despite the capability of certain facultative bacteria like *S. aureus* also forming abscesses, should call to mind anaerobic infection.

- Gas is found in many anaerobic infections.
- Manifestations of disseminated intravascular coagulation are unusual in patients with purely anaerobic infections.

- **Antibiotic susceptibility of Streptococci**

  - **Antibiotic susceptibility of *Streptococcus pneumoniae* (Pneumococcus)**

β-lactam antibiotics are antibiotics of first choice in the treatment of pneumococcal infections. In recent years however, many studies have demonstrated an increasing rate in the resistance *S. pneumoniae* to these antibiotics and many others (Musher, 2005:811; Johnson *et al.*, 2001:S7). Writing on antimicrobial susceptibility of gram-positive bacteria regarding what was current at the time and what should be anticipated Johnson *et al.* (2001:S7), reported findings of an antibiotic resistance surveillance group, SENTRY, which noted increasing resistance rates of 6%, 9% and 22% of pneumococcal isolates to penicillin in 1997, 1998 and 1999 respectively in Europe. According to Johnson *et al.* (2001:S7). The group also reported increasing resistance rates of 15%, 22% and 25% to erythromycin and rather noted a stable rate of resistance of 24 – 25% for tetracycline for the same years. These findings were contrary to what had been the case in the 1960's when practically all clinical isolates of the pathogen were sensitive to penicillin. Currently in the US about 15% and 20% of pneumococcal isolates have been reported to be respectively resistant (minimum inhibitory concentration (MIC) ≥ 2.0 μg/ml) and intermediately susceptible (MIC of 0.1 and 1.0 μg/ml) to penicillin (Musher, 2005:811). Further reports on the susceptibility of this organism in the US as Musher (2005:811) further indicated show that about 25% of all isolates of the pathogen are resistant to erythromycin and the newer macrolides including azithromycin and clarithromycin. A PROTEKT (Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin) United States study actually reported a higher prevalence of 38.8% penicillin resistant strains (Nguyen & Chung, 2005:1145). Blasi *et al.* (2006:363) reported the global rates of *S. pneumoniae* resistance to penicillin and erythromycin in 1996 and 1997 as 10.4 -14.1% and 16.5-21.9%. These rates, their reports noted, respectively increased to 18.2% and 24.6% for the two antibiotics in 1998 and 2000. Much higher resistances of the organism to penicillin and erythromycin have been reported in some specific countries (Blasi *et al.,* 2006:363). A multi-centre international surveillance study performed in the Far East in 1999 – 2000 by PROTEKT

and which investigated the in vitro activity of greater than twenty antibacterial agents against common respiratory pathogens in Hong Kong, Japan, and South Korea for example revealed that *S. pneumoniae* isolates in these countries were 57.1%, 44.5% and 71.5% resistant to penicillin and 71.4%, 77.9% and 87.6% resistant to erythromycin respectively (Inoue *et al.*, 2004:45).

Penicillin–susceptible pneumococci are susceptible to all commonly used cephalosporins while penicillin intermediate resistant strains tend to be resistant to all first and many second generation cephalosporins with most however being susceptible to 3rd generation cephalosporins including cefotaxime, ceftriaxone, cefpodoxime and also the 4th generation member of the group, cefepime (Musher, 2005:811). According to the author, fifty percent of pneumococci highly resistant to penicillin are resistant to cefotaxime, ceftriaxone, cefepime and nearly all are resistant to cefpodoxime.

Musher (2005:811) also noted that approximately one third of pneumococcal isolates exhibit reduced susceptibility to trimethoprim–sulfamethoxazole and that the more recent fluoroquinolones are highly effective against pneumococci. The PROTEKT Far East study group as noted that pneumococci susceptibility to co-trimoxazole and tetracycline decreased with penicillin resistance and that resistance to the fluoroquinolones in the three Far East countries in which the surveillance study was done was generally low. Specifically they reported fluoroquinolone resistances in these three countries as 14.3% for Hong Kong, 2.9% for South Korea and 1.3 % for Japan (Inoue *et al.*, 2004:47). Over all the most active oral antibacterial agents against *S. pneumoniae* by the PROTEKT report were telithromycin, moxifloxacin and linezolide (Inoue *et al.*, 2004:47). Literature reports of patterns of pneumococci resistance in Africa rather seem very limited. Having said this though, it is noteworthy to indicate that the findings of Denno *et al.* (2002:233) as indicated in Section 1.2, and which noted reports of the emergence of *S. pneumoniae* resistance to penicillin and other commonly available antibiotics, notably co-trimoxazole and tetracycline in urban Ghana, is a pointer to the fact that increases of pneumococcal resistance to antibiotics indeed is global and does not exclude African countries.

In summary these reviews on *S. pneumoniae* susceptibility, a pathogen which largely is responsible for many lower respiratory tract infections denote that resistance of the organism to antibiotics which hitherto had been very susceptible to penicillin and other antibiotics is generally on the increase globally and that significant variation in trends of

resistance to pneumococci exists among geographical areas. It is inferred from these that knowledge on local patterns of levels of resistance of the pathogen to various antibiotics is necessary for informed decision making when it comes to presumptive antibiotic selection and prescription for the management of infectious diseases caused by this organism.

- **Antibiotic susceptibility of Group A streptococci (*S. pyogenes*)**

PROTEKT United states data for 2000 to 2001 showed Group A streptococci, *S. pyogenes,* to exhibit 100% sensitivity to penicillin, the antibiotic of choice for the treatment of infections caused by the organism (Nguyen & Chung, 2005:1145). Felmingham *et al.* (2004:49) in their 1999-2000 global PROTEKT surveillance study reported that *S. pyogenes* isolates from children were fully susceptible to a number of antibacterial agents including β-lactam antibiotics and levofloxacin. The author's also reported that approxiamtely 90% of isolates were susceptible to the macrolides erythromycin, clarithromycin and azithromycin which are often used as substitutes for penicillin in treating penicillin sensitive patients with *S. pyogenes* infections. According to Wessels (2005:825) in areas where resistance rates exceed 5 -10%, use of macrolides must be avoided unless results of sensitivity patterns are known. Telithromycin, a new ketolide antibiotic to which *S. pyogenes* demonstrated 99.2% sensitivity, was seen to have a similar degree of efficacy with penicillin irrespective of whether the organism was resistant to erythromycin (Nguyen & Chung, 2005:1145). The antibiotic for this reason and by the authors' indication, can be used instead of the macrolides in penicillin sensitive patients and in areas where pathogen resistance to the organisms have been reported to exceed 5 -10%.

- **Antibiotic susceptibilities of Groups B (*S. agalactiae*), C, D (non – enterococci), G and viridans streptococci**

Group B streptococci are susceptible to penicillin and ampicillin (Inglis, 2003:21) Similarly, all groups C, D (non – enterococci) and G streptococci are sensitive to penicillin (Wessels, 2005:823). Viridans streptococci are usually sensitive to penicillin and erythromycin (Elliot *et al.*, 2004:36). Some strains however have been reported tolerant to penicillin and higher concentrations of this antibiotic may be needed for treating infections caused by them (Inglis, 2003:21).

° Antibiotic susceptibility of Group D streptococci (Enterococci)

The enterococci are becoming increasingly recognised as significant nosocomial opportunists (Johnson *et al.*, 2001:S7). Unlike streptococci they are not reliably killed by penicillin or ampicillin alone at concentrations achieved clinically at blood levels (Wessels, 2005:830). Inglis (2003:245) reported both *E. faecalis* and *E. faecium* as being intrinsically resistant to penicillin. Johnson *et al.* (2001:S7) reported the organisms as generally difficult to eradicate because they both show intrinsic low level resistance to the β-lactams, aminoglycosides and lincosamides. They have high level resistance to aminoglycosides and have remarkable propensity to develop or acquire resistance to other agents including macrolides, tetracyclines, chloramphenicol, quinolones, and glycopeptides (Johnson *et al.*, 2001:S7). Further to the authors' note, glycopeptide resistance of the organism and the spread of these strains of the genus have been observed to be emerging, particularly in the case of *E. faecium* as compared with *E. faecalis*. In the USA, and according to Johnson *et al.* (2001:S8) the resistance of *E. faecalis* in 1995 and 1997 to glycopeptides remained at less than 2% while resistance among *E faecium* isolates rose from 26% to 49%. Data from the United Kingdom (UK) and the SENTRY project, as further reported by Johnson *et al.* (2001:S8), 0.5% and 24% of *E faecalis* and *E. faecium* respectively were resistant to vancomycin in the UK. Without specifying their species composition, the author's also reported that vancomycin resistant enterococci from American hospitals, increased from 14% in 1997 and 1998, to 17% in 1999.

The high probability of enterococci being resistant to most antibiotics as the above review indicates precludes reliance on empiric prescriptions for the treatment of infections in which these organisms are implicated as pathogens. It underscores the need for susceptibility tests to be performed to enable appropriate choices of antibiotics to be made in treating enterococcal infections.

° Antibiotic susceptibility of anaerobic streptococci (Peptostreptococci) and other anaerobic bacteria

This subsection reviews antibiotic susceptibility of anaerobic bacteria in general considering that antibiotic choices in treating anaerobic infections takes into account possible presence of other anaerobic bacteria with which anaerobic streptococci may occur together in mixed infections.

Peptococcus and *Peptostreptococcus*, the principal species of anaerobic streptococci, are usually sensitive to penicillin (Inglis, 2003:21) but their sensitivity to metronidazole is unpredictable (Kasper, 2005:945). In their study of susceptibilities of anaerobic bacterial isolates from intraabdominal infections in Kuwait, Panigrahi *et al.* (2001:294) reported 100% sensitivity of *Peptostreptococcus micros* isolates from these infections to metronidazole and various other antibacterial drugs, notably clindamycin, imipenem, meropenem, cefoxitin, cefoperazone, ceftizoxime, and piperacillin/tazobactam. In California, Goldstein *et al.* (2006:64) also investigated the activities of various antibiotics including metronidazole, penicillin G, amoxycillin/clavulanate, ampicillin/sulbactam, piperacillin/tazobactam, cefoxitin ertapenem, imipenem, chloramphenicol and clindamycin against isolates of *Peptostreptococcus micros*, and reported their sensitivity to these antibiotics as 100%.

Bacteroides spp including *B. fragilis,* the most prevalent of anaerobic bacteria are β-lactamase producers and are all essentially resistant to penicillins and the cephalosporins (Ulger-Toprak *et al.*, 2004:257). In a study in which the researchers determined antibiotic susceptibilities of clinical and human intestinal isolates of *B. fragilis* and B. *thetaiotaomicron* in Turkey, they found over 93% of both organisms from either of the two indicated sources to be β-lactamase producing (Ulger-Toprak *et al.*, 2004:257). Their reported susceptibility test results showed *B. fragilis* to exhibit resistance rates of 98% to ampicillin, 14% to piperacillin and 36% to clindamycin. *B. fragilis* by their findings however was highly sensitive to imipenem (100%), amoxicillin/clavulanate (100%) metronidazole (100%), chloramphenicol (96%) and cefoxitin (89%). Clindamycin, the researchers noted, has been commonly used in treating anaerobic infections. By their report, however, resistance among the *B. fragilis* group to the antibiotic has over the past 20 years been noticed to be increasing in many parts of the world and currently vary between 33% and 43%. In explanation to this they indicated that since microbial resistance to clindamycin is conferred by macrolide-lincosamine-streptogramin B, the clinical use of clindamycin or erythromycin may be responsible for the increased frequency of clindamycin resistance among *Bacteroides* species.

Goldstein *et al.* (2006:64) and Panigrahi *et al.* (2001:294) also reported sensitivities of 100% of *B. fragilis* to metronidazole and piperacillin/tazobactam as well as high sensitivity rates of above 90% for imipenem, meropenem and cefoxitin. The two working groups also reported lower sensitivity rates of the *Bacteroides* species in general to

clindamycin. According to Kasper (2005:945), *Bacteroides* spp including *B. fragilis* generally demonstrate appreciable sensitivity towards combinations of β-lactam antibiotics and inhibitors of β-lactamase, notably, amoxycillin/clavulanic acid, ampicillin/sulbactam, ticarcillin/clavulanic acid and piperacillin/tazobactam combinations.

Resistance rates among *Porphyromonas*, *Prevotella*, and *Fusobacterium* spp to penicillin according to (Kasper, 2005:945) are reported to be increasing rapidly due to β-lactamase production. Up to 60% of clinical isolates of *Prevotella*, *Porphyromonas*, *Fusobacterium* and non-*Bacteroides fragilis* species isolated from infections originating above the diaphragm are now known to produce β-lactamase (Kasper, 2005:945). The organisms are, however, reportedly highly sensitive to metronidazole according to findings of Goldstein *et al.* (2006:64) and Panigrahi *et al.* (2001:294).

Katsandri *et al.* (2006:231) in the literature review for their work in which they determined activities of tigecycline against gram-negative anaerobic bacteria including strains that were resistant to metronidazole in Greece, reported that resistance of gram-negative anaerobic bacteria to metronidazole is increasing world-wide, though in their study they reported a 3 per cent increase which they attributed mainly to *Prevotella* species. The findings of their study established an overall susceptibility rate of 93% of the gram-negative anaerobic isolates they tested to tigecycline and high rates of resistance to clindamycin, cefoxitin and tetracycline. Tigecycline is a relatively new tetracycline and a glycylcycline derivative of minocycline. With their reported 93% susceptibility rate of these pathogens to this antibiotic, they described tigecycline as exhibiting good activity against most gram-negative anaerobic bacteria especially among strains resistant to other anti-anaerobic agents and that it may be considered as an alternative option for infections involving these microorganisms.

Noting that commercially available fluoroquinolones, principally ciprofloxacin and ofloxacin are inactive or marginally active against anaerobes and that fluoroquinolones with enhanced activity against anaerobic bacteria, namely, grepafloxacin and trovafloxacin, have been withdrawn or restricted on the market, Behra-Miellet *et al.*, (2002:366) were motivated to test and compare to other agents the activity of moxifloxacin against clinical anaerobes. Moxifloxacin is a new 8-methoxy fluoroquinolone with established enhanced activity against gram-positive cocci, gram-negative bacilli and atypical agents but without much documentation of its activity

against anaerobes (Behra-Miellet *et al.*, 2002:366). The researchers specifically tested the activity of this antibiotic against clinical strains of *B fragilis* group and clostridia isolated from abdominal infections and blood cultures; *Prevotella, Porphyromonas* and *Fusobacterium* spp isolated from sputum and pleural aspirates and ear and nose and throat infections and compared it with the activities of ciprofloxacin, ofloxacin, clindamycin, cefotetan, imipenem, metronidazole and the β-lactams (amoxicillin, amoxycillin/clavulanate, ticarcillin, ticarcillin/clavulanate). The results of their study established that moxifloxacin unlike other fluoroquinolones, demonstrated high activity against *B. fragilis* and clostridia. In addition to exhibiting excellent activity against gram-positive anaerobic cocci (*Porphyromonas*, *Prevotella* and *Fusbacterium* spp), it is also more potent than ofloxacin and ciprofloxacin against these organisms.

From the above review one can conclude that world-wide speaking, metronidazole glaringly stands out as the most effective of antibacterial agents to use in treating anaerobic gram-negative bacterial infections. Though not current, results of yearly analyses of the spectrum and potency of metronidazole carried out by Erwin *et al.* (2001:231) which reported the overall activity of metronidazole against US clinical anaerobic isolates not changing significantly over their four-year period of testing of these isolates against metronidazole, give some credence to this conclusion. It must be noted, however, that the agent is inactive towards aerobic and facultative bacteria and that it should not be prescribed alone in the event of these organisms being implicated in infections caused by anaerobic bacteria (Kasper, 2005:945). Tigecycline and moxifloxacin by the results of studies indicated above, are promising alternatives for use in anaerobic infections particularly in mixed infections of these bacteria with other pathogens, e.g. gram-negative or facultative aerobes, against which metronidazole is not effective.

- **Antibiotic therapy of streptococcal associated infections**

  - **Antibiotic therapy of *Streptococcus pneumoniae* (Pneumococcus) infections.**

Otitis media and acute sinusitis

The pathogenesis and microbial aetiology of otitis media and acute sinusitis are similar and their diagnosis is most of the time presumptive (Musher, 2005:811). In an empiric treatment of these infections it is important to note, according to the author, that apart from *S. pneumoniae* being an obvious target organism, *Haemophilus influenzae* and

Moraxella catarrhalis are also very frequently implicated as aetiological agents of these infections and that many strains of these organisms are β- lactamases producing. Also, high serum levels of antimicrobial agents are required to treat otitis caused by intermediate or resistant pneumococci because of the need of the antibiotic to penetrate into an enclosed space to be effective against the microbes. For these reasons, and also for reasons that antibiotics that resist β-lactamases despite their effectiveness against pneumococci are expensive, the Centre for Disease Control (CDC) according to Musher (2005:811) further, recommends that the following approach be adopted in treating otitis media and acute sinusitis:

- High dose **amoxicillin** (80 - 90 mg/kg in two to three divided doses for infants and toddlers or 1 gm three times daily for adults) or
- **Amoxycillin/clavulanic** acid combination with the amoxicillin given in the same doses as without clavulanic acid in the event of amoxicillin alone failing as in the case of β-lactamase producing organisms being present.
- Alternatively, the Centre recommends the use of **ceftriaxone, quinolones** or a **ketolide** in the treatment of the infection.

The American Academy of Paediatrics in addition to the high dose use of amoxicillin or its combination with clavulanic acid also recommends the use of second generation cephalosporins such as **cefuroxime** or a **macrolide** antibiotic in patients allergic to penicillins. Pneumococcal resistance patterns also indicate that sulfamethoxazole/trimethoprim (Co-trimoxazole) or erythromycin/sulfisoxazole combinations are not likely to be useful in patients who do not respond to amoxicillin (Garau & Dagan, 2003:1947).

Pneumonia

β-lactam antibiotics are the main antibiotics for the treatment of pneumococcal infections of which community acquired pneumonia is a notable example (Musher, 2005:811). This said, however, and for the many other organisms involved in the aetiology of the infection, as well as the reported increasing resistance of *S. pneumoniae* to the penicillins, the empiric prescribing of antibiotics, particularly the penicillins in treating community acquired pneumonia has become highly inadequate. This underscores the need to determine or investigate the precise aetiology of the infection before antibiotic treatment is attempted (Musher, 2005: 809). Commonly however, antibiotics are presumptively prescribed in acute pneumonia. The selection of whatever antibiotic is

prescribed in such cases is in principle, done on "best guess" basis in a syndromic approach in which the microbial cause of infection may not have to be named before antibiotic therapy is initiated (Inglis, 2003: 76).

Meningitis

Third generation cephalosporins (TGCs) are effective against most isolates of pneumococci according to Musher (2005:813). The drugs also cross the blood brain barrier very easily unlike vancomycin, for example, which has unpredictable capacity in crossing this physiological barrier. Vancomycin on the other hand is reported to be effective against most isolates of the pathogen. On the basis of this, Musher (2005:813) recommended treatment of pneumococcal meningitis with **ceftriaxone** (1- 2 g every 12 hrs) or **cefotaxime** (2 g every 6 hrs) or **imipenem** (500 mg every 6 hrs) in the event of patient reaction to the β-lactams, plus **Vancomycin** (500 mg every 6 hrs or 1 g every 12 hrs). Instead of vancomycin, Inglis (2003:130) recommended the use of **chloramphenicol** in a double antibiotic therapy of the infection.

Endocarditis

Endocarditis, though rare, is associated with rapid destruction of heart valves. Its diagnosis should be promptly treated with the initiation of **ceftriaxone or cefotaxime** plus **vancomycin** in view of the increase in resistant strains of the organism pending availability of results of susceptibility investigations (Musher, 2005:813).

Summary of Antibiotic choice in pneumococcal infections

In summary one can conclude from the above reviews that, pending results of susceptibility studies, except if local patterns of pneumococcal susceptibility to antibiotics suggest otherwise, infections with *S. pneumoniae* should be preferably treated presumptively with high dose **β–lactam antibiotics** (penicillin G, amoxycillin or ampicillin), **third generation cephalosporins** (ceftriaxone or cefotaxime) with **vancomycin** added where necessary to ensure effective coverage of resistant strains of the pathogen. **Quinolones**, particularly the more recent fluoroquinolones (**gatifloxacin** and **levofloxacin**) and the **ketolides** could also be used. Use of co-trimoxazole must be avoided in presumptive treatment of pneumococcal infections because of the high rate resistance of the pathogens to the antibiotic (Musher, 2005:811).

° **Antibiotic therapy of Group A streptococci (*S. pyogenes*) infections**

Infections of group A streptococci are generally treated with penicillin, an antibiotic to which the pathogens still remain very susceptible (Elliot *et al.,* 2004:33). In patients sensitive to penicillin, erythromycin is generally used as a substitute. Wessels (2005:825,826) recommended the following regimens for various streptococcal infections.

- **Pharyngitis and Impetigo**: **Benzathine penicillin** G 1.2 mU IM for adults or **penicillin V** 250 mg three times daily or 500 mg twice daily for 10 days. In the case of streptococcal impetigo, penicillinase resistant antibiotics like **cloxacillin/dicloxacillin** may be preferably used in treating the infection for reasons of covering as well *S. aureus* which often complicates such infections

- **Erysipellas/Cellulitis**: **Penicillin G**, 1 - 1.2 mU IV every 4 hrs or **Procaine penicillin** 1.2 mU IM twice daily (Wessels, 2005:825).

- **Necrotizing fasciitis/myositis**: **Penicillin G** 1.2 mU IM for adults or **penicillin V** 250 mg three times daily or 500 mg twice daily for 10 days plus **clindamycin** 600 - 900 mg every 8 hours for reasons of covering pathogens like anaerobic organisms other than streptococci (Wessels, 2005:825). Inglis (2003) suggested a combination of **ampicillin**, **gentamicin** and **metronidazole** for presumptive treatment of necrotising fasciitis (Inglis, 2003:62)

- **Pneumonia/empyema:** Penicillin G 2-4 mU IV every four hours
- **Streptococcal toxic syndrome: Clindamycin** initially and followed if necessary **penicillin G** 2-4 mU IV every 4 hours (Clindamycin inhibits protein synthesis and hence the production of pyrogenic exotoxins that are responsible for the syndrome) (Wessels, 2005:828)

° **Antibiotic therapy of Groups B (*S. agalactiae*), C, D (non enterococcal), G, and Viridans (α-haemolytic) streptococci**

Other streptococci like *S. pyogenes* are appreciably susceptible to the β-lactam antibiotics and generally therefore these antibiotics have remained the drugs of choice in the treatment of infections caused by these organisms (Elliot *et al.*, 2004:36).

Penicillin or **erythromycin** in the case of penicillin sensitive patients in particular is the antibiotic of choice for the treatment of Group B streptococcal (*S. agalactiae*) infections (Elliot *et al.*, 2004:33; Wessels, 2005: 829) and for bacterial sepsis caused by the pathogens, empiric broad spectrum antibiotics consisting of **ampicillin** and **gentamicin** are recommended (Wessels, 2005: 829). The treatment of bacterial endocarditis requires antibiotic combinations e.g. penicillin plus gentamicin (Elliot *et al.*, 2004:36).

Groups C and G streptococci infections are treated with **penicillin** as the antibiotic of choice in the same way as patients with Group A streptococcal (*S. pyogenes*) infections are treated (Wessels, 2005:829).
Like other streptococci, **penicillin**, (**erythromycin** for penicillin sensitive patients) is the antibiotic of choice for infections with viridans streptococci (Elliot *et al.*, 2004:36) For reasons of some strains of the group being tolerant to penicillin higher concentrations of this antibiotic may be needed to ensure effective treatment of infections caused by these organisms (Inglis, 2003: 245). Neutropenic patients with viridans streptococci bacteraemia are often resistant to penicillin and it is recommended to treat such patients with **vancomycin** presumptively pending susceptibility testing results (Wessels, 2005:831).

- **Antibiotic therapy of Group D streptococci (Enterococci)**

In vitro testing has demonstrated evidence of synergistic killing of most enterococci by a combination of **penicillin** or **ampicillin** with **aminoglycosides** (Wessels, 2005:830). Based on this, Wessels (2005:831), recommends the combined therapy of these antibiotics, with a substitution of vancomycin for the β-lactam antibiotic in penicillin sensitive patients, in the treatment of serious enterococcal infections like enterococcal endocarditis or meningitis. For reasons of ampicillin reaching sufficiently high urinary concentrations, he also recommends the use of ampicillin in a mono-therapy antibiotic treatment of uncomplicated enterococcal urinary tract infections. **Nitrofurantoin** or **trimethoprim** is usually satisfactory for enterococci urinary tract infections and is also recommended for treating urinary tract infections (Inglis, 2003:245). These recommendations being made amidst increasing reports of ampicillin resistant *E. faecium* and gentamicin and vancomycin – resistant *E. faecalis* (Inglis, 2003:245) underscores the importance of relying on local antibiotic sensitivity patterns and the routine performance of susceptibility testing tests in patients with serious enterococcal infections for effective antibiotic treatment (Wessels, 2005:831).

Antibiotic therapy of anaerobic streptococci (Peptostreptococci) and other anaerobic bacteria associated infections

Penicillin and metronidazole are antibiotics of choice in the treatment of anaerobic streptococci associated infections (Elliot *et al.*, 2004: 37; Inglis, 2003: 245). With the sensitivity of these organisms to metronidazole being reported as unpredictable, however, penicillin may be considered the sole antibiotic of choice in treating infections of anaerobic streptococcal infections (Kasper, 2005:945). In view of the high possibility of other anaerobic bacteria occurring in mixed anaerobic infections with peptostreptococci, it is prudent when treating infections of anaerobic streptococci presumptively to take into consideration antibiotic coverage of these other anaerobic pathogens. Anaerobic bacteria that need to be considered in these circumstances include *Bacteroides*, *Fusobacterium*, *Prevotella, Porphyromonas, Clostridium* and *Propionibacterium* spp. Kasper (2005:945), recommends the following antibiotics for presumptive treatment of anaerobic bacterial infections:

- **Penicillin** plus **Metronidazole** for less serious infections with **Clindamycin** as an alternative;
- **Imipenem**; and
- **Ampicillin/sulbactam** or **Amoxycillin/clavulanic acid** or **ticarcillin/clavulanic acid** or **Piperacillin/tazobactam** in penicillin resistant infection.

Aminoglycosides or quinolones (Moxifloxacin) are shown to have in vitro activity against many anaerobes) in resistant infections

2.1.4.2 *Staphylococcus* spp

Staphylococcus aureus, S. epidermidis or *S. albus* and *S. saprophyticus* are three clinically important members of *Staphylococcus* spp of which there are at least 20. *S. aureus* is the most virulent of staphylococcal species. It characteristically produces coagulase enzyme which enables it to coagulate plasma. This property distinguishes it from other staphylococci which do not produce this enzyme and are collectively referred to as *coagulase negative staphylococci* (CoNS) (Elliot *et al.,* 2004: 25; Inglis, 2003: 243)

- **Morphological characteristics and epidemiology**:

Staphylococci are gram-positive cocci that display as grapelike clusters on Gram's stain. They are catalase producing (unlike streptococci), non motile, non – sporing, non

capsulate and grow over a wide temperature range of about 10 – 42°C under both aerobic and facultative anaerobic conditions of oxygen requirement (Elliot *et al.,* 2004: 25; Lowy, 2005:814).

Staphylococci are normal commensals of human hosts. *S. aureus* for example colonises up to about 50% of healthy persons mainly in the anterior nares. Colonisation may also occur on damaged skin, vagina, axilla, perineum and oropharynx and at a rate higher among insulin dependent diabetic patients, HIV-infected persons, injection drug users, patients undergoing haemodialysis and individuals with skin damage (Lowy, 2005:814). *S. epidermidis* is found on the skin, where it is the most abundant bacteria species, and also in the oropharynx and the vagina. *S. saprophyticus* is a pathogen of the urinary tract (Lowy, 2005:820; Elliot *et al.*, 2004:29).

- **Mechanisms of Staphylococcal pathogenesis**:

S. aureus is a pyogenic pathogen known for its capacity to produce disease because of its ability to invade tissues and form abscesses at both local sites and sites of metastasis (Lowy, 2005:814). It produces extracellular enzymes or exotoxins and combat host defences (Elliot *et al.,* 2004:27). Staphylococci are opportunistic pathogens with the initiation of their infection requiring a breach in cutaneous or mucosal barriers. At the initial stage of their infection they elicit an inflammatory response characterised by an intense production of polymorphonuclear leukocytes that is followed by infiltration of infected tissues by macrophages and fibroblasts (Lowy, 2005:815). As the pathogen replicates at the onset of infection, it elaborates enzymes and toxins that aid its penetration and invasion of tissues as well as its evasion of host defence systems. It elaborates for example, proteases, hyaluronidases, and lipases which respectively degrade proteins, dissolve hyaline and solubilise lipids, and also coagulase enzyme which causes fibrin deposition and a resultant interference of phagocytosis (Todar 2009:4; Elliot *et al.*, 2004:27). It also produces exotoxins such as leucocidin and the haemolysins α and β toxins which contribute to its virulence. Leucocidin lyses leukocytes including PMNs, macrophages and monocytes while haemolysins lyse erythrocytes and damage platelets (α toxin), degrade sphingomyelin and demonstrate toxicity towards many cells including erythrocytes (β toxin). These effects of the elaborated enzymes and toxins facilitate survival of the pathogen and promote its invasion of tissues (Elliot *et al.*, 2004:27). Phagocytes and endothelial cells are also capable of internalising

staphylococci and providing sanctuary that protects the bacteria against host defence systems. Microbial cellular internalisation also results in host cellular changes like the expression of integrins and the release of cytokines which may contribute to systemic manifestations of disease including sepsis and vasculitis (Lowy, 2005:816).

As Lowy (2005:816) stated, staphylococci also possess an antiphagocytic polysaccharide microcapsule and most *S. aureus* infections are due to the organism's possession of microcapsules types 5 and 8. These are characterised with the presence in them of both negatively and positively charged molecules (zwiterionic charge pattern) which are considered critical to abscess formation. The microbe according to the authors also has a unique cell wall protein, protein A, which binds a component of IgG (immunoglobulin G) antibody, the F_c component, and protects it from opsophagocytosis by PMNs. Binding of protein A to F_c component of IgG also allows complement activation and manifestation of some of the symptoms associated with the infection. Apart from its ability to invade tissues and cause disease, certain clinical manifestations of *S. aureus* infections are mediated through toxins that it elaborates. Significant among these are enterotoxins, staphylococcal toxic shock syndrome (TSS) toxin, and exfoliative toxins (Lowy, 2005:816). Enterotoxins and TSS toxin as Lowy (2005: 816 further stated, are respectively responsible for staphylococcal food poisoning and toxic shock syndrome. They are both small molecular size proteins that act like superantigens inducing an uncontrolled proliferation of T cells in a process that involves their direct stimulation of antigen presenting cells without their prior processing as foreign proteins by the antigen presenting cells for controlled T cell production. The uncontrolled proliferation or overexpansion of T cell is accompanied by over production of cytokines and the release of inflammatory mediators such as interferon γ, interleukin-1, interleukin-6, TNF-α and TNF-β resulting in a multisystem disease that may clinically manifest as myalgias, fever, rash and hypotension. Enterotoxins also stimulate the vagus nerve and the vomiting centre of the brain to cause the characteristic symptoms of food poisoning, namely diarrhoea and vomiting. Exfoliative toxins, disrupt desmosomes that link adjoining cells to trigger exfoliation or superficial desquamation (Lowy, 2005:816; Elliot *et al.,* 2004:27).

CoNS are the most common causes of prosthetic device infections with *S. epidermidis* as the most commonly implicated in these types of infections among the group. It is uniquely adapted to colonise these devices by its capacity to produce extracellular

polysaccharide that forms biofilm on the device surface and protects the organism from antibiotics and host defences. *S. saprophyticus* by its possession probably of 160-kDa haemaglutinin/adhesion has enhanced capacity to adhere to uroepithelial cells and remains basically an organism of urinary tract infections (Lowy, 2005:820).

- **Staphylococcal associated infections**:

S aureus is associated with listed infections listed below..

- **Skin and soft tissue infections**: In the presence of predisposing factors such as skin diseases, damage to the skin, injections and poor personal hygiene *S. aureus* causes a variety of cutaneous skin infections characterised by the formation of pus-containing blisters. These include, and in order of severity, **folliculitis**, **furuncles** (or boils) and **carbuncles.** Folliculitis is superficial and involves the hair follicle. Furuncles and carbuncles are characterised with pus discharging from blisters. Other skin and soft tissue infections include **mastitis** which is characterised by clinical manifestations that range from cellulitis to abscess formation with fever and chills often present in more severe cases, **impetigo** (an acute infection of the superficial epidermis demonstrating as painless lesions progressing from confluent vesicles and pustules to dried out yellow crusts), **cellulitis** (an acute spreading infection of the skin and subcutaneous tissues) and **hydradenitis suppurativa** (recurrent follicular infections in regions such as the axilla) and **wound infections**. *S. aureus* is a common cause of surgical wound infections (Lowy, 2005:817; Elliot *et al.*, 2004:28; Inglis, 2003: 57 & 58).

- **Musculoskeletal infections**: *S. aureus* is a common cause of osteomyelitis (bone infections characterised by fever and pain in the bone), septic arthritis (characterised with fever and pain and swelling in the affected joint) and pyomyositis (an infection of the skeletal muscle which often presents with fever, swelling and pain (Lowy, 2005:818; Elliot *et al.,* 2004:28).

- **Respiratory tract infections**: *S. aureus* associated respiratory tract infections (RTI) occur only in selected clinical settings which include severe RTI in newborns and infants. They present with shortness of breath, fever and respiratory failure, pneumothorax and empyema; nosocomial RTI in intubated patients on intensive care units; RTIs occurring in community patients as sequelae to post viral infections

and characterised by bloody sputum production (Lowy, 2005:818; Elliot *et al.,* 2004:28). Pneumonia due to methicillin resistant *Staphylococcus aureus* (MRSA) strains are associated with such specific factors as intubation and prolonged mechanical ventilation, length of hospitalisation or prolonged stay in intensive care units as well as previous broad-spectrum antibacterial treatment (Ferrara, 2007:19).

- **Septicaemia and Infective endocarditis:** *S. aureus* associated bacteraemia is complicated with sepsis, vasculitis, endocarditis and metastatic seeding that demonstrates as suppurative collections at other tissue sites such as brain, liver, spleen, kidneys, lungs and joints (Lowy, 2005:818; Elliot *et al.,* 2004:28).

- **Urinary tract infections:** *S. aureus* rarely cause urinary tract infections (UTI). It may result occasionally from instrumentation of the genitourinary tract (Lowy, 2005:819). *S. epidermidis* occasionally causes urinary tract infections particularly in catheterised patients (*Elliot et al.*, 2004: 28) while *S. saprophyticus,* accounting for 15% of common pathogens implicated in uncomplicated UTI (Stamm, 2002:1S) is associated with urinary tract infections in sexually active women occasionally resulting in severe cystitis with haematuria (*Elliot et al.*, 2004: 29)

- **Prosthetic device related infections:** *S. aureus* is commonly implicated in prosthetic device related infections involving intravascular catheters, prosthetic valves, orthopaedic devices, peritoneal or intraventricular catheters and vascular grafts. Unlike the more subtle infections of coagulase negative staphylococci (CoNS), S aureus prosthetic device related infections characteristically presents acutely with both localised and systemic manifestations and are more progressive (Lowy, 2005:818; Elliot *et al.,* 2004:28).

- **Toxin mediated diseases:** Some diseases associated with *S. aureus* according to Lowy (2005:819) are outcomes of host exposure to toxins elaborated by the pathogen. These include **toxic shock syndrome** (TSS), **food poisoning** and **staphylococcal scalded-skin syndrome** (SSSS). They are associated respectively with toxic shock syndrome toxin-1 (TSST-1), enterotoxins and exfoliative toxin. TSS is a multisystem disease involving the liver, kidneys, gastrointestinal tract and the central nervous system. The patient initially presents with non-specific flu like symptoms including fever, hypotension and erythroderma

which then rapidly progresses to a multiple of symptoms that includes vomiting, diarrhoea, confusion, myalgias and abdominal pain. Laboratory findings may show azotemia, leukocytosis, hypoalbuminaemia and liver function abnormalities. Staphylococcal enterotoxin food poisoning is characterised by rapidity of onset (1 - 6 hours after ingestion of toxins in food) and the absence of fever. Main symptoms are nausea and vomiting though diarrhoea, dehydration and hypotension may also present. SSSS syndrome often affects newborns and children. Its main feature is the formation of localised blisters that progress to exfoliation or desquamation of much of the skin surface (Lowy, 2005:819; Elliot *et al.*, 2004:28).

- **Staphylococcal antibiotic susceptibility**

According to Lowy (2005:821), more than 95% of strains of staphylococci produce penicillinase. This makes the majority of the pathogens resistant to the penicillins except the semi-synthetic penicillinase resistant penicillins (SPRP) such as oxacillin, nafcillin, cloxacillin or flucloxacillin. Some strains of *S. aureus* sensitive to the SPRPs, the author indicated are now, however, resistant to methicillin, the first member of the SPRPs. These are referred to as methicillin resistant *Staphylococcus aureus* (MRSA) and are seen to form about 40% – 50% of all isolates of *S. aureus* in many hospitals. MRSAs are also characteristically resistant to all other SPRPs and the cephalosporins, and many other antibiotic families including the quinolones, aminoglycosides and macrolides.

In an epidemiological and antibiotic susceptibility study in which Jones *et al.* (2003:408) carried out susceptibility tests on MRSAs isolated from skin and soft tissues infections in the USA and Europe it was found out, for example, that apart from vancomycin to which 100% of isolates were susceptible, only co-trimoxazole and gentamicin showed ≥70% activity against MRSA. The majority of MRSA, the researchers observed, crossed resistance to other antibiotics tested including amoxycillin/clavulanate, cefotaxime, and ceftriaxone to which the isolates showed 100% resistance and ciprofloxacin and erythromycin to which they were respectively 83.9% and 87.8% resistant. Their findings of the researchers, however, predictably showed all methicillin susceptible *Staphylococcus aureus* (MSSA) and methicillin susceptible coagulase-negative *Staphylococcus aureus* (MS-CNS) to be susceptible to the 3rd generation cephalosporins and amoxicillin/clavulanate. They also found 4.5% to 12.1% of MSSA isolates from countries from which isolates were obtained to be resistant to ciprofloxacin.

In another study in which Brown and Ngeno (2007:223) investigated antimicrobial resistance in clinical isolates of *Staphylococcus aureus* from hospital and community isolates in southern Jamaica all MRSA isolates tested for their antibiotic susceptibility were 100% sensitive to vancomycin, 33.3% resistant to co-trimoxazole and gentamicin and tetracycline and 16.7% resistant to ciprofloxacin and nitrofurantoin.

While the above reports have favourably shown MRSAs to be very susceptible to vancomycin to depict this antibiotic as the answer to MRSA infections, it is noted that strains of MRSA found to have reduced susceptibility to or are completely resistant to vancomycin (VISA strains) have now been isolated (Lowy, 2005:821). In his review of reduced glycopeptide susceptibility in MSRA, Appelbaum (2007:399) reported the appearance of several case reports of VISA in Europe, Asia and the USA following the second case report of the isolation of this strain of *S. aureus* in Japan in 1997, the first being in 1996 also from the same country. To indicate the rapidity with which VISA is becoming problematic, Appelbaum (2007:399) also reported of a recent report from a single hospital in Turkey in which 256 MRSA isolates from clinical specimens of hospitalised patients obtained between 1998 and 2001 yielded 46 isolates of VISA strains. These had higher minimum inhibitory concentrations of 5-9 μg/ml and were accordingly termed hVISA strains.

S. epidermidis isolated from hospital patients is often resistant to semi-synthetic penicillinase resistant penicillins and erythromycin. and necessitates the use of glycopeptides e.g. vancomycin in the treatment of *S. epidermidis* infections among the (Elliot *et al.*, 2004:28).

- **Antibiotic therapy in staphylococcal infections**

Selection of antimicrobial agents in the treatment of *S. aureus* is similar to that of other staphylococci (coagulase negative staphylococci). Generally therefore antibiotic selection for the treatment of staphylococcal infections follows patterns of antibiotic selection in the treatment of *S. aureus* infections. Lowy (2005:821) and Elliot *et al.* (2004:28) accordingly recommended the following as antibiotic treatment options for *S. aureus* and hence other staphylococcal infections.

- **Penicillin sensitive strains**: Penicillin G
- **Penicillin resistant strains**: SPRPs (e.g. nafcillin, oxacillin, cloxacillin or flucloxacillin), erythromycin, all generations of cephalosporins and carbapenem - imipenem formulations.

- **MRSAs**: Vancomycin (glycopeptide) is the antibiotic of choice in treating methicilin resistant staphylococci with minocycline, co-trimoxazole, the quinolones, quinupristin/dalfopristin and daptomycin being used as alternatives in the event of vancomycin intolerance or toxicity.
- **VISA strains**: Quinupristin/dalfopristin (streptogramin) has bactericidal activity against all strains of staphylococci including VISA strains.

Of particular note in the therapy of MRSA associated infections is the difficulty in treating MRSA pneumonia. Outlining treatment of hospital-acquired pneumonia caused by MRSA, Ferarra (2007:21) indicated that vancomycin which is used as the first line of treatment in MRSA associated infections has only modest efficacy in lung infection because of the failure of the drug to reach adequate concentrations in lung tissue due to its high protein binding in plasma. This makes the antibiotic rather inefficient in treating MRSA associated pneumonia. Drugs of potential interest which may have a place in the management of severe MRSA pulmonary infection the author mentioned include tigecycline, a glycylcycline and analogue of tetracycline, ceftobiprole, a novel parenteral cephalosporin and telavancin, a novel lipoglycopeptide. Few options for treatment of MRSA pneumonia as of present include the oxalidinones as exemplified by linezolid and the streptogramins of which quinupristin/dalfopristin (Ferarra, 2007:21).

2.1.4.3 *Clostridium* spp

- **Morphological characteristics and epidemiology.**

Clostridia are gram-positive bacilli spore forming obligate anaerobes that are found in soil and the gastrointestinal tracts of mammals (Elliot *et al.*, 2004:38). Four species principally are of medical importance and these according to the authors include *Clostridium perfringens, C. tetani, C. botulinum* and *C. deficille*. *C. perfringens* the most abundant of clostridia has five major strains designated A through E. Type A which produces predominantly the enterotoxin, α-toxin, predominates in faecal flora of humans as well as soil and is associated mostly with human infections. Types B, C, D, and E, produce other toxins in addition to α-toxin. They inhabit gastrointestinal tract of animals and are associated mainly with animal infections. *C. perfringens* ferments a variety of sugars with gas production (Elliot *et al.*, 2004:38; Kasper & Macdoff, 2005:845).

- **Mechanisms of Clostridial pathogenesis**

Pathogenesis of *Clostridium* species is mainly through toxin elaboration (Kasper & Macdof, 2005:845). Growth of the pathogens as indicated by the authors requires about 14 amino acids and 6 additional growth factors which are found mainly in necrotic tissue but not in body fluids. These limit clostridial infections mainly to necrotic tissues and are not significant aetiologies of bacteraemic infections (Kasper & Macdof, 2005:845). *C. perfringens* as the authors further indicated, possesses 17 possible virulence factors, including 12 active tissue toxins and enterotoxins. Alpha toxin (α-toxin), one of the major enterotoxins responsible for the pathogenicity of the organism, is associated with the development of gas gangrene. It is known to be haemolytic, to destroy platelets and Polymorphonuclear leucocytes and to cause widespread capillary damage. Another toxin of *C. perfringens*, θ toxin also known as perfringolysin O, has also been shown to play an important role in the pathogenesis of the organism. The toxin promotes vascular leukostasis, endothelial cell injury, and regional tissue hypoxia. Together, these cause perfusion defects that extend the anaerobic environment conducive for pathogen growth and the resultant rapid destruction of tissue. Both α and θ toxins are also responsible for the near absence of PMNs in gas gangrene. The toxins induce leukocyte aggregation at the margins of tissue injury instead of their expected infiltration into the area of damage. Other major toxins, notably β, ε, and ι toxins are known to increase capillary permeability (Stevens & Bryant, 2002:S93; Kasper & Madoff, 2005:845).

C. botulinum according to Abrutyn (2005: 843) elaborates eight distinct types of toxins designated A, B, C_1, C_2, D, E, F, and G. All are neurotoxins except C_2 which is a cytotoxin with unknown clinical significance. The neurotoxins are known for their blockade of transmitter release from peripheral cholinergic nerve endings and hence their ability to cause neuroparalytic illness. They get access to the blood stream and then to cholinergic nerve endings when they get absorbed from the gastrointestinal tract when food contaminated by *C. botulinum* is eaten or when ingested spores of the pathogen germinate and grow to produce the toxins in the gastrointestinal tract. The toxins also could be absorbed into the blood when they become elaborated in wound by infecting *C. botulinum*

C. tetani produces the neurotoxin, tetanospasmin. The toxin binds to peripheral motor neuron terminals, enters the axon and gets transported to the nerve cell body in the brain stem and spinal cord by an intraneuronal transport system. In the brain the toxin

blocks release of inhibitory neurotransmitters glycine and γ-aminobutyric acid (GABA). This results in an increase in the resting firing rate of α-motor neurons resulting in the production of characteristic muscle rigidity seen in tetanus. Loss of CNS inhibition due to lessened glycinergic or GABA activity may also affect preganglionic sympathetic neurons in the lateral gray matter of the spinal chord and produce sympathetic hyperactivity to cause high levels of circulating catecholamines. Tetanospasmin also blocks acetylcholine release at neuromuscular junctions to cause muscle weakness and paralysis (Abrutyn, 2005:840)

C. deficille produces two toxins responsible for its pathogenesis. These include toxin A, an enterotoxin, and toxin B, a cytotoxin. The two toxins initiate processes responsible for the disruption of epithelial-cell barrier function to result in diarrhoea and pseudomembrane formation. They glucosylate proteins that regulate the actin cell cytoskeleton to cause its disruption. Disruption of the cytoskeleton results in loss of cell shape, cell adherence and cell tight junction integrity to cause fluid leakage and the formation of pseudomembranes as seen in the diarrhoea and the colonic pseudomembranes associated with *C. dfficille* associated disease. Infections of *C. difficile* occur as a result of exposure to antimicrobial agents and the consequent disruption of the normal colonic flora. (Gerding & Johnson, 2005: 760,761; Elliot *et al.,* 2004: 40)

- **Clostridial associated infections and their clinical presentations**

In association with other anaerobic bacteria, *C. perfringens* commonly causes suppurative deep tissue infections such as intraabdominal sepsis, empyema, pelvic abscess, subcutaneous abscess, frostbite gas gangrene, infection of a stump in an amputee, brain abscess, prostatic abscess, perianal abscess, conjunctivitis infection of renal cell carcinoma, and infection of an aortic graft. The pathogen is also invariably associated with skin and soft tissue infections including anaerobic cellulitis, a localized infection with necrosis but no systemic signs of toxicity. The pathogen is also involved in a fatal form of cellulitis and fasciitis that spreads rapidly with signs of systemic toxicity. The syndrome differs from necrotizing fasciitis caused by other organisms mainly by the rapidity of its mortality and tissue invasion and the systemic effects of the toxin. (Kasper & Madoff, 2005: 846).

Gas gangrene, a myonecrotic infection characterized by rapid and extensive necrosis of muscle accompanied by gas production and systemic toxicity is a disease of *C. perfringens* infection. Other members of the genus implicated in the causation of the infection are *C. noyvii* and *C. septum* (Inglis, 2003: 247) Gas gangrene occurs when bacteria invades healthy muscle from adjacent traumatized muscle or soft tissue. An essential factor in the genesis of gas gangrene appears to be trauma, particularly involving deep muscle laceration. The trauma need not be severe but the wound must be deep, necrotic and without communication to the surface (Kasper & Madoff, 2005: 847).

C. perfringens, primarily type A, is also a known causative organism of food poisoning. With symptoms that include epigastric pain, nausea and watery diarrhoea usually lasting 12 to 24 hours. The organism has also been implicated in more severe forms of diarrhoea than that of classic food poisoning (Kasper & Madoff, 2005: 845).

C. butulinum, through presynaptic inhibitory effects of its elaborated neurotoxins is noted for its causation of flaccid paralysis of respiratory and facial muscles (Inglis, 2003:248) Inhibition of cranial nerves almost always marks the onset of symptoms which clinically demonstrates as diplopia, dysarthria, dysphonia and/or dysphagia. Weakness progresses rapidly form the head to involve the neck, arms, thorax and legs. Paralytic ileus, severe constipation and urinary retention are also commonly seen in the infection (Abrutyn, 2005:843).

C. tetani infection of wound results in the elaboration by the organism of the neurotoxin tetanospasmin and the development of tetanus (Elliot *et al.*, 2004:40), a disease characterised by generalised muscle rigidity or spasms. Common symptoms are dysphagia or stiffness or pain in the neck, shoulder and back muscles following increased tone in the masseter muscles. Rigid abdomen and stiff proximal limb muscles may flow as a result of subsequent involvement of other muscles (Abrutyn, 2005:840).

Clostridium deficille disease is the major known cause of nosocomial diarrhoea and is an emerging cause of nosocomial diarrhoea (Balagopal & Sears, 2007:455). The infection of the pathogen uniquely causes colonic infection that is exclusively associated with a disruption of normal colonic flora through antimicrobial use. The disease is characterised with the development of diarrhoea and colonic pseudomembranes. The use of all antibiotics may result in colonic *C. difficile* infection but the second and third generation

cephalosporins, principally, cefuroxime, cefotaxime, ceftriaxone, are agents now noted as being most often implicated in the development of the condition. Clindamycin and ampicillin were among the first antibiotic associated *C. difficile* infections. The pathogens are acquired exogenously, most often in the hospital and are carried in the stool of symptomatic and symptomatic patients. The rate of faecal colonisation is often greater than 20% among adult patients hospitalized for greater than one week, which in contrast, is 1 – 3% among community residents (Gerding & Johnson , 2005: 760).

- **Antibiotic susceptibility of Clostridia**

Clostridial pathogens are generally sensitive to penicillin and metronidazole (Inglis, 2003: 247) but there are reports of increasing resistance to penicillin by *C. perfringens,* the causative agent for gas gangrene. Other antibiotics the organisms are frequently but not universally susceptible to include cefoxitin, carbenicillin, chloramphenicol, clindamycin, doxycycline, imipenem, minocycline, tetracycline, third generation cephalosporins and vancomycin (Kasper & Madoff, 2005: 848).

C tetani is susceptible to penicillin and metronidazole (Inglis, 2003: 247) *C. difficile* on the other hand is resistant to many β-lactam antibiotics but is sensitive to vancomycin, metronidazole and bacitracin (Inglis, 2003: 248).

- **Antibiotic therapy of clostridial associated infections**

For treatment of clostridial infections Kasper and Madoff (2005:848) suggested the following choices of antibiotics.

Gas gangrene and Clostridial sepsis:
Penicillin plus **clindamycin** with **chloramphenicol, metronidazole, imipenem** or, and in the event of penicillin allergy, **doxycycline** as alternative antibiotics after sensitivity testing.

Suppurative deep tissue infections:
Penicillin plus **gentamicin** or a **3rd generation cephalosporin** (e.g. **ceftriaxone**) or in the event of penicillin sensitivity, gentamicin plus any of the alternative antibiotics after sensitivity testing as in the treatment of gas gangrene or clostridial sepsis (Kasper & Madoff, 2005:848) *C. difficile* associated disease may resolve within 2 - 3 days after

withdrawal of the precipitating antimicrobial agent according to Wilcox (2003:486). **Metronidazole** or **vancomycin** given orally and in respective doses of 400 mg three times daily or 125 mg four times daily for 10 days, are however the authors treatment of choice. Symptomatic recurrences following *C. difficile* infections are common, but it is not known however whether such high failure rates of treating the infections are due to relapses or re-infections. Currently courses of 4 to 6 weeks with tapering and pulsed doses of vancomycin are used to in theory to first kill vegetative bacteria, to allow spores to germinate and then be killed (Wilcox, 2003:486).

2.1.4.4 Corynebacterium spp

Morphological characteristics and epidemiology

Corynebacterium are commensals of man (Elliot *et al.*, 2004:42). Of members of the species, *Corynebacterium diphtheriae* according to Lagrou *et al.* (1999:7) is the most important pathogen responsible for respiratory infection with neurological complications in man. Other members of the group which have been increasingly reported as opportunistic pathogens in nosocomial infections include *C. jeikeium* and C. *urealyticum* (Lagrou *et al.*, 1999:7). By descriptions of Elliot *et al.* (2004:42), they are non-capsulate, non-sporing, gram-positive aerobic rods and are found inhabiting the upper respiratory tract. They are club shaped and are arranged in clusters or parallel arrays on growth media. Their cultivation requires use of selective media containing either tellurite or collistin plus nalidixic acid (Holmes, 2005:832) to suppress the growth of other upper respiratory tract commensals without an effect on growth of *C. diphtheriae*.

- **Mechanisms of Corynebacterium pathogenesis**

Toxigenic strains of *C. diphtheriae* are not invasive. They multiply locally in the pharynx and elaborate an exotoxin that destroys epithelial cells to result in acute inflammatory reactions through a mechanism involving inhibition of cellular protein synthesis (Elliot *et al.*, 2004: 43). Systemic dissemination of the toxin results in cardiac- and neurotoxicity (Inglis, 2003:247; Elliot *et al.,* 2004: 43) and possible focal necrosis in various organs including the kidneys, liver and adrenal glands (Holmes, 2005: 833).

- **Corynebacterium associated infections and their clinical presentations**

C. diphteriae is the cause of respiratory diphtheria, an upper respiratory tract infection characterised with inflammatory exudate in the oropharynx (Inglis, 2003:246). The infection is often complicated with cardiac and neurological pathology which clinically manifests as myocarditis and polyneuropathy (Elliot *et al.*, 2004:42; Holmes, 2005: 833). *C. urealyticum* is predominantly a pathogen of the urinary tract. *C. amycolatum*, the most common species among infection related strains of *Corynebacterium* is associated with wound infections and infections related to the blood and the urinary tract. C. *jeikeium* is believed to be associated with infections in immunocompromised persons (Lagrou *et al.*, 1998:10)

- **Corynebacterium antibiotic susceptibility**

Lagrou *et al.* (1999:7). carried out susceptibility test on many strains of *Corynebacterium* in a study conducted to identify and investigate the clinical relevance and antibiotic susceptibility of coryneform organisms in clinical specimens in a University Hospital in Belgium in 1997. Their findings revealed *C. jeikeium* as the most multidrug-resistant strain among the species. The majority of the strains were resistant to the β-lactam antibiotics, macrolides, gentamicin, ofloxacin and fusidic acid. All isolates investigated were found to be 100% susceptible to vancomycin and teicoplanin. *C. amycolatum* and *C urealyticum* the other clinically important members of the species generally show resistances of between 75%-89% to the β-lactam antibiotics and between 50% and 84% to erythromycin, clindamycin, gentamicin, ofloxacin and rifampicin. Of the two strains of the pathogens, *C. amycolatum* showed higher resistance to these antibiotics. Plasmid mediated resistance of *C. diphtheriae* to erythromycin had been reported to have emerged transiently during an epidemic in Seattle but these have declined with the discontinuation of the use of erythromycin (Holmes, 2005: 835).

- **Antibiotic therapy in Corynebacterial infections**

Respiratory diphtheria is treated with diphtheria antitoxin. Antibiotics have little effect on the healing of local infection in diphtheria patients treated with antitoxin. Goals of antibiotic treatment are to eradicate the pathogen and prevent transmission from infected patients to susceptible persons. Recommended for these uses are **erythromycin** given orally or by injection for 14 days or **procaine penicillin** given intramuscularly for 14 days. **Rifampicin** and **clindamycin** are also successfully used

and are acceptable alternatives to penicillin or erythromycin in patients who cannot take these antibiotics (Holmes, 2005:835; Elliot *et al.*, 2004:43).

Prevention of diphtheria infections is achieved through the practice of regular immunization schedules. Diphtheria vaccination is part of the routine immunization of children in most developed countries (Elliot *et al.*, 2004:43). Diphtheria and tetanus toxoids and acellular pertusis vaccine adsorbed (DtaP) is currently recommended for all doses in primary immunization schedule for children up to age 7 years. Tetanus and diphtheria toxoids adsorbed (Td, for adult use) is currently recommended for routine booster immunization at 10-year intervals in adults who do not have contraindications. Td is also recommended for adults who require prophylactics for tetanus prone wounds (Holmes, 2005:835).

2.1.5 Gram-negative bacterial pathogens: Pathogenesis, antibiotic susceptibilities associated infections and recommended treatments

This section reviews the pathogenesis, antibiotic susceptibilities, associated infections and recommended treatments of infections caused by gram-negative bacterial pathogens. Pathogens that appear to be regularly isolated at study site microbiology laboratories and atypical pathogens associated commonly diagnosed infections received attention in this section of the review.

2.1.5.1 Gram-negative cocci

Most commonly encountered gram-negative cocci in medical practice belong to the genera *Neisseria* and *Moraxella*, with *N. gonorrhoea*, *N. meningitidis* and *M. catarrhalis* being the medically important members of the group (Inglis, 2003:252)

2.1.5.1.1 *Neisseria* spp

- **Morphological characteristics and epidemiology**

N. gonorrhoea (gonococcus) is a coffee bean shaped, non-motile, non-spore forming and aerobic gram-negative organism that grows in pairs (diplococci). It can be differentiated from other *Neisseria* spp by their ability to grow on selective media and to utilise glucose but not maltose, lactose or sucrose (Ram & Rice, 2005:855). *Neisseria*

meningitidis (meningococcus) is kidney shaped. In addition to other common features it shares with *N. gonorrhoea* it has a polysaccharide capsule (Stephens *et al.*, 2005: 849) which, apart from its shape, morphologically differentiates it from the former.

Neisseria spp are obligate parasites of man and are found inhabiting mucus membranes of the genitourinary and respiratory tracts. *N. gonorrhoea* organisms are harboured by asymptomatic females from whom transmission of the pathogen is carried through sexual contact (Elliot *et al.,* 2004: 48). *N. meningitidis*, being normal commensals of respiratory tract are predominantly transmitted through respiratory secretions (Stephens *et al.*, 2005: 849).

- **Neisseria pathogenesis**
  - ***Neisseria gonorrhoea* (gonococcus)**

Gonococci have cell surface frimbriae (pilli) which facilitate the adherence of the pathogens to mucosa and account greatly for the virulence of the organisms, (Elliot *et al.,* 2004:48). Ram and Rice (2005:856) indicated the presence on urogenital epithelial cells in both men and women membrane co-factor proteins, CD46 cells, which serve as receptors for the protein subunit, PilC, located at the tips of the gonococcus pilus molecules. In addition to these PilC protein subunits, and further to the authors' description of pathogenesis of the pathogens, are also a number of other gonococcal proteins that probably contribute to the virulence and pathogenesis of the organism according to the authors. These as they indicated, include opacity associated protein (Opa), a surface protein, which is considered important in the adherence of the pathogens to epithelial cells. Opa is known to promote inter-gonococcal adhesion, adherence of gonococci to eukaryotic cells including polymorphonuclear leukocytes and the invasion of epithelial cells by the pathogens.

Other surface proteins notably porin, the most abundant of gonococcal surface proteins and also transferrin- and lactoferrin binding proteins are gonococcal proteins that have further been indicated by Ram and Rice (2005:856) as playing major roles in the organisms' virulence and pathogenesis. Porins, as the authors mentioned, exhibit antigenic variations that have been used to serotype gonococci basically into two types of strains, namely, Por1A and Por1B. Of the two types of strains, Por1A strains of the pathogen resist killing action of normal human serum and are associated with disseminated gonococcal infection with less ability to induce local genital infections due

to their inability to induce significant inflammatory response. Por1B strains on the other hand are killed by normal human serum. They have ability to induce significant inflammatory response and are responsible for and confined only to local genital infections. Gonococci deficient in transferrin- and lactotransferrin binding proteins have been shown to be unable to establish infections in men. This suggests that the presence of these proteins in and hence the acquisition of iron by gonococci might be essential for the establishment of their infections (Ram & Rice, 2005:856).

Apart from possession of virulence surface proteins, and like other gram-negative organisms, gonococci also have a type of lipooligosaccharide that possesses marked endotoxic activity and contributes to local cytotoxic effects in cells infected by the organisms. *N. gonorrhoeae* also elaborates immunoglobulin A1 (IgA1) protease which may protect the organism from the actions of mucosal IgA (Ram & Rice, 2005:856).

- ***Neisseria meningitidis*** **(meningococci)**

In their description of *Neisseria meningitidis* Stephens *et al.* (2005:849) stated that meningococci colonizing the upper respiratory tract are internalized by non-ciliated mucosal cells which may then cross them into the submucosal cells from which they may make their way into the blood stream. According to them, pathogens entering the blood from the nasopharynx this way and surviving host defences may multiply either slowly or rapidly. Slowly multiplying organisms they indicated often seeds local sites such as the meninges, and less frequently, the joints and the pericardium and cause infections at these sites. Rapidly multiplying bacteria in the blood are associated with the clinical features of meningocaemia which includes petechiae, purpura, disseminated intravascular coagulation and shock which may precede the seeding and ultimate infections of other body tissues (Stephens *et al.,* 2005: 849).

Stephens *et al.* (2005:849) and also Elliot *et al.* (2004:68) attributed the virulence of the meningococci to its capsular polysaccharides and outer membrane proteins. The capsules impart antiphagocytic and antibactericidal properties to the meningococcus and enhance the organism's survival during invasion of the bloodstream or cerebrospinal fluid. Like gonococci, meningococci are piliated and easily adhere to epithelial cell surfaces during colonisation. They are also capable of acquiring the iron carrying molecules, transferrin and lactotransferrin, a property as studies with gonococci demonstrated, may be essential for the organism's capability of causing infections.

Meningococci also express lipooligosaccharides (LOS), a type of lipopolysaccharides as expressed by many other gram-negative bacteria (Stephens *et al.*, 2005:851). The lipid moiety of meningococcal LOS which is the pathogen's endotoxin mediates the induction of inflammatory cytokines responsible for the inflammation associated with meningococcal infectious diseases. The morbidity and mortality of meningococcal bacteraemia and meningitis for example correlates directly with the amount of circulating meningococcal endotoxin (Stephens *et al.*, 2005:851).

- **Neisseria associated infections**

Neisseria gonorrhoea is a cause of sexually transmitted infectious diseases in both men and women, often clinically demonstrating as purulent inflammatory conditions of genitourinary anatomical structures (Ram & Rice, 2005:857).

In males gonococcal infections commonly presents as acute urethritis that develops 2 to 7 days after exposure. The urethritis is usually more severe and overt than those of non-gonococcal urethritis, including urethritis caused by *Chlamydia trachomatis*. It is often impossible, though, to differentiate between gonococcal and chlamydial urethritis on clinical grounds alone. (Ram & Rice, 2005:857) Complications of gonorrhoea in men according to the authors, include epididymitis and prostatitis but these are rare probably because of the promptness with which majority of men contracting the disease seek medical attention. Other complications may include oedema of the penis due to dorsal lymphagitis or thrombophlebitis, periurethral abscess or fistulae inflammation or abscess of Cowper's gland, and seminal vesiculitis).

In females gonococcal infections further to Ram and Rice's (2005:857) descriptions of the infections, present as mucopurulent cervicitis with a yellowish or greenish mucus (mucopus) discharging from the cervical os. Women who remain asymptomatic or have only minor symptoms which may include scant discharge from the vagina and dysuria without urgency or frequency, often delay seeking medical attention. Symptoms of the infection which usually develop within 10 days after exposure are very similar to those of *Clamydia trachomatis* infections but are more intense and acute than the latter. Gonococcal infections in women may ascend into the upper genitourinary structures and cause such complications as pelvic inflammatory disease (PID) which may present as acute dyspareunia or painful coitus, lower abdominal or back pain, endometritis with menstrual bleeding and salpingitis when spread to the fallopian tubes occurs (Ram &

Rice, 2005: 858,859). Gonococcal infections may also involve non-genital anatomical areas as exemplified by such infections as.

- anorectal gonorrhoea when the infection spreads to the anus and rectum particularly in females whose anatomy permits easy spread of the infection to the anal areas;;
- pharyngeal gonorrhoea which may result from oral genital sexual exposure;
- ocular gonorrhoea resulting from autoinoculation from an infected genital area;
- ophthalmia neonatum which results from exposure of the new born to infected cervical secretions; and
- gonococcal arthritis involving the large joints and which may result from gonococcal bacteraemia.

As indicated by Stephens *et al.* (2005:852,853), *Neisseria meningitidis* is associated primarily with meningococcaemia and meningitis and most often all two types of meningococcal infections may demonstrate in the patient at the same time. Meningococcaemia is associated with fever, chills, nausea, vomiting and myalgias with rash as a distinctive feature. The rash characteristically begins as erythematous macules that rapidly become petechial and in severe cases, purpuric. The lesions are typically found on the trunk and lower extremities but they may also occur on the face and arms and mucous membranes. Presenting symptoms of meningococcal meningitis include nausea and vomiting, headache, neck stiffness, lethargy and confusion. They are not distinguishable from those of other meningeal pathogens but in patients in whom the condition occurs together with meningococcaemia, characteristic rash accompanying the latter will be indicative of a correct diagnosis

.

- **Neisseria antibiotic susceptibility**

N. gonorrhoea has become resistant to numerous antibiotics because of its remarkable capacity to alter its antigenic structure and adapt to changes in the microenvironment. The organisms' development of resistance to antibiotics is by mechanisms attributable to either chromosomal mutations or acquisition of plasmids. It may involve their development of the ability to produce β-lactamase (penicillinase) or alter their penicillin binding proteins to become resistant to penicillins or β-lactam antibiotics. Additionally they may also undergo chromosal mutations that may confer on them resistance to antibiotics (Ram & Rice, 2005:856).

Penicillin resistance caused either by β-lactamase production or by altered penicillin binding proteins and also tetracycline and even quinolone resistances are seen with increasing frequency among *N. gonorrhoea* (Inglis, 2003:253). Stathi *et al.* (2007:S306) who also investigated antimicrobial susceptibility of gonococci isolated in Greece in 2005 reported finding a dramatic increase of between 11.3% – 33.3% in the resistance of *N. gonorrhoea* to the quinolones, norfloxacin and ciprofloxacin.

Studying antibiotic susceptibility of *Neisseria gonorrhoea* in men with urethral discharge in Malawi, Zachariah *et al.* (2002:234) reported that none of the antibiotics tested in their study approached the WHO recommended 95% sensitivity for effective "blind treatment". Specifically their results showed that out of the 47 isolates of *N. gonorrhoea* they investigated, 85% were susceptible to gentamicin and spectinomycin, 68% to ciprofloxacin and 45%, 26%, 5% and 2% to erythromycin, co-trimoxazole, tetracycline and penicillin respectively.

β-lactamase production had also been noted among *Neisseria meningitidis* in recent years (Inglis, 2003:253). High level penicillin resistance particularly has been reported and, there are reports generally of increasing prevalence of meningococci with reduced susceptibility to penicillin (Stephens *et al.*, 2005: 853). These notwithstanding, Inglis (2003:253) considered penicillin resistance of *Neisseria meningitidis* to be rather uncommon .Resistance of the pathogens to the extended-spectrum cephalosporins e.g. cefotaxime and ceftriaxone that are most frequently used antibiotics for the treatment of invasive meningococcal disease in developed countries has not been reported (Tzanakaki & Mastrantonio, 2007:621).

Despite its widespread use in developing countries as a standard therapy of meningococcal infections in the developing countries, chloramphenicol is still remarkably active against *Neisseria meningitidis.* Resistance of the pathogen to this antibiotic, though, has been reported from Vietnam, France and Australia where 12 chloramphenicol resistant strains from Vietnam and 1 each of same strains from the latter two countries have been reported (Tzanakaki & Mastrantonio, 2006:621). The newer fluoroquinolones (gatifloxacin, moxifloxacin and gemifloxacin) also have very excellent activity against *Neisseria meningitidis*.

- **Antibiotic therapy in Neisseria infections**

° **Gonococcal infections**

Highly effective single dose treatments have been developed for the treatment of uncomplicated urogenital gonococcal infections to promote compliance and ensure effective eradication of infecting pathogens. Because of co-infection with *C. trachomatis* initial treatment regimens incorporates in principle an agent effective against this pathogen as well. Table 2.4 is a compilation of antibiotics and their doses recommended in the treatment of gonococcal infections according to 2002 Guidelines of the Centers for Disease Control and Prevention (Ram & Rice, 2005: 861; Holmes, 2005:765, 771).

° **Meningococcal (*N. meningitidis*) Infections**

Meningitis and meningococcaemia syndromes are treated with **third generation cephalosporins** (e.g. **Cefotaxime** 2 g IV every 4 hrs or **Ceftriaxone** 2 g IV every 12 hrs) (Stephens *et al.*, 2005:853). Added to a cephalosporin of choice may also be other antibacterial agents that may cover other bacteria acting as possible etiologic agents of meningitis. **Penicillin** is as an acceptable alternative for confirmed cases of meningococcal infections but with a note of caution amidst reports of reduced susceptibility of meningococci to penicillin (Stephens *et al.*, 2005:853). Other options listed by the authors include **Meropenem** 1 g IV every 8 hrs and **Chloramphenicol** 75 – 100 mg /kg daily

For empiric treatment of meningitis Roos & *Tyler* (2005:2475) noted that cefotaxime and ceftriaxone also provide coverage for susceptible *S. pneumoniae*, group B streptococci and *H. influenzae* which are agents other than *N. meningitidis* capable of causing same syndromes. The authors also indicated that due to emergence of penicillin-and cephalosporin-resistant strains of *S. pneumoniae*, the most common etiologic organism of community-acquired bacterial meningitis next to *N. meningitidis,* empirical therapy of community–acquired bacterial meningitis in children and adults should include **Vancomycin**.

Table 2.4 Recommended treatments for Gonococcal Infections: 2002 Guidelines of the Center for Disease Control and Prevention (Ram & Rice, 2005:861)

Diagnosis	Treatment of Choice
Uncomplicated gonococcal infection of the cervix, urethra, pharynx or rectum with possible co-infection with *Clamydia trachomatis*	
First Line regimen	Ceftriaxone (125 mg IM, single dose) OR Ciprofloxacin (500 mg PO, single dose) OR Ofloxacin (400 mg PO, single dose) OR Levofloxacin (250 mg single dose) OR Cefixime (400 mg PO, single dose PLUS Azithromycin (1 g PO, single dose or Doxycycline (100 mg PO bid for 7 days)
Alternative regimens	Spectinomycin (2 g IM single dose) OR Ceftizoxime (500 mg IM, single dose) OR Cefotaxime (500 mg IM, single dose) OR Cefotetan (1 g IM, single dose, with Probenecid 1 g PO, single dose) OR Cefoxitin (2 g IM, single dose, with Probenecid 1 g PO, single dose) PLUS Azithromycin (1 g PO, single dose OR Doxycycline (100 mg PO bid for 7 days)
Epididymitis	Ceftriaxone (250 mg IM, single dose) THEN Doxycycline (100 mg orally bid for 10 days) OR Ofloxacin (300 mg PO bid for 10days) OR Levofloxacin (500 mg PO q 24 hrs for 10 days
Pelvic inflammatory disease: **Outpatients** Regimen A Regimen B	 Ofloxacin 400 mg PO for 14 days OR Levofloxacin (500 mg PO qd for 14 days PLUS Metronidazole 500 mg PO bid for 14 days Ceftriaxone (250 mg IM single dose) PLUS Doxycycline (100 mg PO bid for 14 days) PLUS Metronidazole (500 mg PO bid for 14 days)
Inpatients Parenteral therapy initiated with either of the following regimens until 48 hrs after clinical improvement and then changed to outpatient therapy Regimen A Regimen B	 Cefotetan (2 g IV q12 hrs) OR Cefoxitin (2 g IV q 6hrs) PLUS Doxycycline (100 mg IV or PO q12 hrs) Clindamycin (900 mg IV q 8 hrs PLUS Gentamicin, loading dose of 2mg/kg IV or IM, then maintenance dose of 1.5 mg/kg q 8 hrs
Gonococcal conjunctivitis in adult	Ceftriaxone (1 g IM, single dose)
Ophthalmia neonatorum	Ceftriaxone (25-50 mg/kg, single dose not to exceed 125 mg)

Disseminated gonococcal infection	
Initial therapy	
Patient tolerant to β-lactam drugs	Ceftriaxone (1 g IM or IV q 24 hrs) OR Cefotaxime (1 g IV q 8 hrs) OR Ceftizoxime (1 g IV q 8 hrs)
Patient allergic to β-lactam drugs	Ciprofloxacin (500 mg IV q 12 hrs) OR Ofloxacin (400 mg IV q 12 hrs) OR Levofloxacin (500 mg IV q 12 hrs) OR Spectinomycin (2 g IM q 12 hrs) OR
Continuation therapy	Ciprofloxacin (500 mg PO bid) OR Ofloxacin (400 mg PO bid) OR Levofloxacin (500 mg PO qd) OR Cefixime (400 mg PO, bid)

Table 2.5 Antibiotics used in empirical therapy of bacterial meningitis and focal CNS infections (Roos & Tyler., 2005: 2475)

Indication	Antibiotic
Preterm infants to infants < 1 month	Ampicillin + Cefotaxime
Infants 1- 3 months	Ampicillin + Cefotaxime Or Ceftriaxone
Immuno-competent children > 3 months and adults < 55 years	Cefotaxime or Ceftriaxone + Vancomycin
Adults > 55 and adults of any age with alcoholism or other debilitating illness	Ampicillin + Cefotaxime or Ceftriaxone + Vancomycin
Hospital acquired meningitis, posttraumatic or Post-neurosurgery meningitis, neutropenic patients or Patients with impaired cell mediated immunity	Ampicillin + Ceftazidime + Vancomycin

The authors also recommended the addition of **Ampicillin** to the empirical regimen for the coverage of *Listeria monocytogenes* in individuals less than 3 months and greater than 55 years of age or those with suspected impaired cell-mediated immunity because of chronic illness, organ transplantation, pregnancy, malignancies or immunosuppressive therapy (Roos & Tyler, 2005: 2475). *Staphylococcus aureus* and gram-negative organisms including *Pseudomonas aeruginosa* are commonly implicated in meningitis acquired in the hospital, particularly after neurosurgical procedures. For the empiric treatment of this category of patients with meningitis it is recommended to add **Vancomycin** and substitute **Ceftazidime** for either cefotaxime or ceftriaxone, in the antibiotic treatment regimen for reasons of ceftazidime being the only cephalosporin with adequate activity against CNS infection with *P. aeruginosa* (Roos & Tyler, 2005: 2476). Table 2.5 provides a list of antibiotics used in empirical therapy of bacterial meningitis and focal CNS infections according to Roos & Tyler, (2005:2775).

2.1.5.1.2 *Moraxella* spp

Moraxella catarrhalis [formerly designated at various times as *Micrococcus catarrhalis, Neisseria catarrhalis* and *Branhamella catarrhalis* according to Musher (2005:862)] is the most common clinically important member of the species (Inglis, 2003:253).

- **Morphological characteristics and epidemiology**

M. catarrhalis is a gram-negative coccus sometimes found as part of normal flora in the nasopharynx and has the ability to cause infection in structures adjacent to the upper respiratory tract or become opportunistic pathogen in the lower respiratory tract (Inglis, 2003:253).

- **Mechanisms of Moraxella Pathogenesis**

A review by Karalus and Campagnari (2000:550) on *M. catarrhalis* as a human pathogen outlined results of many studies that showed the organism as having a number of outer membrane proteins (OMPs) that contribute to its virulence. Some of these proteins coded and known as CopB, OMP CD, UspA1 and UspA2 and OMPE according to the authors, have largely been recognised to play essential roles in the pathogenicity of *M. catarrhalis*.

CopB has been observed for example to bind to human lactoferrin to suggest that this OMP is involved in iron acquisition and or utilization from human lactoferrin, a process known to be essential for bacterial growth and replication and progression of infection (Koczura & Kaznowski, 2003:197). According to the authors, antibodies directed against CopB enhanced the clearance of the organism from the lungs of animals and suggested that the OMP is very likely to be important in the host immune response to *M. catarrhalis*. Available data also suggested the OMP UspA1 to be essential for the attachment of *M. catarrhalis* to host epithelial cells. The putative function of UspA2 appears to be associated with the resistance of *M. catarrhalis* to the bactericidal activity of normal sera. The organism also has pili or fimbriae that might be involved in its attachment to epithelial cells.

Apart from the apparent involvement of CopB in iron acquisition and utilization by the pathogen, *M. catarrhalis* as Karalus and Campagnari, (2000:550) further indicated is also known to have transferrin and lactoferrin binding proteins, TbpA and TbpB, and LbpA and LbpB, which act as receptors for the pathogens acquisition and utilization of iron from the host.

Like other gram-negative human mucosal pathogens principally *Neisseria meningitidis, N. gonorrhoeae* and *Haemophilus influenzae, M. catarrhalis* also possesses surface lipooligosaccharides with epitopes that share homology with lipooligosaccharide epitopes with these other mucosal pathogens. Lipooligosaccharides are known to be important virulence factors for infections caused by these organisms (Musher, 2005:862; Karalus & Campagnari, 2000:550).

- **Moraxella associated infections**

M. catarrhalis is a significant cause of middle ear infection in both infants and young children and is recognised as one of the three major causes of otitis media and sinusitis along with *Streptococcus pneumoniae* and *Haemophilus influenzae.*(Karalus & Campagnari, 2000:547). As opportunistic pathogens they cause acute exacerbations of chronic bronchitis with increased production of purulent sputum and purulent tracheobronchits and pneumonia in older adults or adults with long history of cigarette smoking, chronic obstructive pulmonary disease, lung cancer and evidence of malnutrition.

M. catarrhalis may also cause bacteraemia with no apparent focal infection in children less than 10 years or adults greater than 60 years of age (Musher, 2005:862). Most such patients are either immunocompromised or have underlying lung disease (Musher, 2005:862; Inglis, 2003:253) *Moraxella* spp may also be associated with wound infections following animal bites as demonstrated by a recent study by Talan *et al.* (1999:88) which found *Moraxella* species including *M. catarrhalis* in infected wounds following 35% and 10% of cat and dog bites.

- **Moraxella antibiotic susceptibility**

Most strains of *M. catarrhalis* (>94%) are currently β- lactamase producing and are penicillin resistant (Inglis, 2003: 253). The enzymes show less activity against cephalosporins and made the organisms demonstrate less such resistance against this β- lactam antibiotics (Inglis, 2003: 253; Musher, 2005:863, Karalus & Campagnari, (2000:550). In the United States, *Moraxella* are found to be uniformly sensitive to tetracycline, the newer macrolides, the ketolides, quinolones, trimethoprim–sulfamethoxazole and chloramphenicol (Musher, 2005:863).

- **Antibiotic therapy in Moraxella infections**

According to Musher, (2005:863) tetracycline and co-trimoxazole may be used in exacerbations of bronchitis due to *Moraxella* infections

Being that pneumococci resistant to these agents may also be implicated in pneumonia in which *M. catarrhalis* are causative etiologic agents the author indicates that in such infections it is more appropriate to use β-lactam antibiotic/β-lactamase inhibitor combinations e.g. **ampicillin/sulbactam** and **amoxicillin/clavulanic acid**, or third generation cephalosporins (**Cefotaxime** and **Ceftriaxone**) or quinolone antibiotics, are effective alternatives.

2.1.5.2 Gram-negative bacilli (GNB)

Pathogenic gram-negative bacilli (GNB) are composed principally of enteric Enterobacteriaceae or enteric bacilli (Elliot *et al.,* 2004:51), environmental bacilli (Inglis, 2003:249) and Parvobacteria (Elliot *et al.,* 2004:57).

Enterobacteriaceae or enteric bacilli (also known as coliforms) are a group of gram–negative bacteria commonly found in the intestinal flora of humans and other animal

species as well as inanimate environment particularly where sewage or manure has been disposed. They ferment glucose, are oxidase negative and grow on blood agar in the presence of bile salts under both aerobic and anaerobic conditions and are hence referred to as facultative anaerobes. (Inglis, 2003: 248; Elliot *et al.,* 2004:51). Medically important members of the group include *Escherichia coli*, *Klebsiella*, *Enterobacter*, *Serratia*, *Proteus*, *Salmonella, Shigella* and *Yersenia* spp. The genera *Escherichia*, *Klebsiella, Enterobacter* and *Serratia* ferment lactose to produce acid and subsequent colour change of a pH indicator to give pink colonies on Mac Conkey agar (Elliot *et al.,* 2004:12). *Salmonella*, *Shigella* and *Proteus* do not ferment lactose and form pale colonies on Mac Conkey agar (Elliot *et al.,* 2004: 51).

Environmental GNB are found in various locations in the inanimate environment including soil, water and many locations in the hospital. They do not ferment glucose and some are strongly oxidase positive. Medically important members of the group recognised as common causes of hospital acquired infections, include *Pseudomonas*, *Acinetobacter*, *Burkholderia* and *Stenophomonas* species (Inglis, 2003:249).
Parvobacteria are a group of GNB that are characteristically small. They have variable shape and are hence referred to coccobacilli. Examples of members of the genera include *Haemophilus, Bordetella, Legionella, Pasteurella* and *Francicella* spp. They grow only on enriched media. (Elliot *et al.,* 2004:57)

2.1.5.2.1 Escherichia coli

The genus *Escherichia* contains only one species, *Escherichia coli,* (Elliot *et al.* 2004:51). This however, has evolved to produce specific strains of the organism that are intestinal pathogens as distinguished from a second type of the genus which are extraintestinal pathogens and cause disease outside the bowel with other GNB (Russo, 2005:878). As with all GNB, *E. coli* according to Elliot *et al.* (2004:52) have lipopolyscaccharides (endotoxins) which when liberated results in complement activation, intravascular coagulopathy and endotoxic shock. They also release as the authors further mentioned, exotoxins that are responsible for diarrhoeal diseases associated with enteropathogenic forms of the pathogens. Thus, and although they are known commensals of the human intestine, *E. coli* can cause a variety of important

infections including, infections of the gastrointestinal tract, urinary tract , biliary tract, lower respiratory tract and septicaemia (Elliot *et al.*, 2004:52).

2.1.5.2.1.1 Intestinal pathogenic *E. coli*

Intestinal pathogenic *E. coli* are not found as part of the normal flora of the gastrointestinal tract (Russo, 2005:878). They have specific virulence factors distinct from those of extraintestinal pathogenic *E. coli* and other GNB which facilitate their adherence to mucosal cells, invasion of into underlying tissue and causation of alterations in mucosal function (Russo, 2005:878; Inglis, 2003: 248) Ingestion of intestinal pathogenic *E. coli* by the naïve host results in colonisation and the development of enteritis, enterocolitis and colitis. Depending on the types of intestinal diseases they cause, they can be sub-classified, according to Russo (2005:878), into pathogenic types, that includes Shiga toxin-producing *E. coli* (STEC) or enterohaemorrhagic *E. coli* (EHEC); Enterotoxigenic *E. coli* (ETEC); Enteropathogenic *E. coli* (EPEC); Enteroinvasive *E. coli* (EIEC); Entero aggregative *E. coli* (EAEC); and Diffusely adherent *E. coli* (DAEC). These are described with their pathogenesis as follows:

- **Shiga toxin-producing *E. coli* (STEC) or enterohaemorrhagic *E. coli* (EHEC).**

These produce the shiga toxins (Stx2 and Stx1) or related toxins that cause haemorrhagic colitis and haemolytic-uraemic syndrome (HUS) (Russo, 2005:878). The toxins have enzymatically active subunits that cleave off adenine from ribosomal ribonucleic acid (rRNA) and irreversibly inhibit ribosomal function. Additional virulence factors of the pathotypes include their acid tolerance and the possession of fimbriae that facilitates their adherence to mucosal surfaces.

STEC and EHEC colonise the large bowel prior to causing diarrhoea (Madappa & Go, 2009:1). Such colonisation of the colon by the pathogens according to Russo (2005:878) results in symptoms after 3 or 4 days. Hallmark of STEC colonic infection the author indicated is bloody diarrhoea after initial secretory diarrhoea that presents without fever. STEC colonic infection can be complicated with HUS (Madappa & Go, 2009:1). This occurs 2 – 14 days after the onset of diarrhoea following a systemic translocation of the shiga toxins to the small vessel, renal and cerebral endothelial cells. Main features of HUS include some fever, thrombocytopenia, renal failure and encephalopathy (Russo,

2005:878) *Shigella* spp causing enterohaemorrhagic colitis may also be implicated in HUS (Inglis, 2003:176).

Domesticated ruminants, particularly cattle and young calf serve as major reservoirs of STEC (Russo, 2005:878). Ground beef according to the author, is a most common food source that gets contaminated with the pathogens during processing. This *E. coli* pathotype by further indications of the author generally cause infection in the developed countries, where consumption of processed food is more common than in the developing countries.

- **Enterotoxigenic *E. coli* (ETEC)**

These produce both heat labile (LT-1) and heat stable (STa) toxins and are causes of endemic diarrhoea in tropical countries particular in children within the first three years of life (Russo, 2005:879). It is a most common cause of travellers' diarrhoea (Madappa & Go, 2009:1). The toxins cause net fluid secretion through activation of adenylyl cyclase (LT-1) and/or guanylyl cyclase (STa) in the jejunum or ileum, resulting in watery diarrhoea and cramps (Russo, 2005:879). STa toxin as the author further noted binds to guanylyl cyclase C found in the brush border of membranes of intestinal epithelial cells to cause increased intracellular concentration of cyclic GMP and the induction of secretory diarrhoea. No histopathologic changes of the small bowel occur in ETEC induced diarrhoea, neither is there any fever nor the production and appearance of mucus, blood and inflammatory cells in the stool.

- **Enteropathogenic *E. coli* (EPEC)**

EPEC causes diarrhoeal disease primarily in infants and is an important cause of this condition in developing countries (Madappa & Go, 2009:1; Russo, 2005:879). Diarrhoeal stools typical of enteropathogenic contain mucus but not blood (Russo, 2005:879). Colonisation of the small bowel according to Madappa and Go (2009:1) occurs prior to casing diarrhoea.

- **Enteroinvasive *E. coli* (EIEC)**

EIEC shares many clinical features with *Shigella*, causing dysentery that very much resembles that caused by the latter (Madappa & Go, 2009:1). Unlike shigella, the organisms produce disease only at a large inoculum. They colonise the large bowel (Madappa & Go, 2009:1) after an initial induction of small bowel secretory diarrhoea due

to elaborated enterotoxins (Russo, 2005:879). Colonisation of the large bowel is followed by the invasion of the colonic mucosa to result in the development of inflammatory colitis characterised by fever, abdominal pain, tenesmus and scant stool containing mucus, blood and inflammatory cells (Russo, 2005:879).

- **Enteroaggregative *E. coli* (EAEC) and Diffusely adherent *E. coli* (DAEC)**

These strains of intestinal pathogenic *E. coli* cause diarrhoea in young children in developing countries as well as travellers' diarrhoea in persons who travelled to endemic areas. Clinical disease has been associated with prolonged watery diarrhoea. (Madappa & Go, 2009:1; Russo, 2005:879).

2.1.5.2.1.2 Extraintestinal pathogenic *E. coli* (ExPEC)

Extraintestinal pathogenic *E. coli* is often found as part of normal human intestinal flora and do not cause intestinal infections (Russo, 2005: 881). These strains of the pathogen according to the authors cause infection when colonising forms, for example, in the colon, the vagina or oropharynx, enter normally sterile sites e.g. the urinary tract, peritoneal cavity or lungs. ExPEC strains have acquired genes that encode for diverse extraintestinal virulence factors that enable the bacteria to cause infections outside the gastrointestinal tract. All age groups, all types of hosts and nearly all types of organs and sites are susceptible to infection by ExPEC. *E. coli* is the most common enteric gram-negative species to cause extraintestinal infection in ambulatory, long term care and hospital settings (Russo, 2005 881).

- **Infections associated with extraintestinal pathogenic *E. coli* (ExPEC)**

  - **Urinary tract infections**

The urinary tract is the site most commonly infected by ExPEC. The pathogen ranks as the most prevalent for all UTI syndrome/host group combinations. In the United States ExPEC accounts for 85 to 95% of an estimated 6 to 8 million episodes of uncomplicated cystitis in menopausal women (Russo, 2005 881). Ronald (2002:14) writing on the aetiology of urinary tract infections indicated *E. coli* as the predominant uropathogen with an 80% rate of isolation, followed by *S. saprophyticus* (10 -15%). Specific bacterial virulence factors markedly influence the likely hood of a given strain of bacteria causing urinary tract infections once introduced into the bladder (Stamm, 2005:1716).

Specifically, as Stamm (2005:1716) stated, most uropathogenic strains of *E. coli*, (typically specific O, K, and H serogroups) that cause urinary tract infections have virulence genes closely linked on bacterial chromosomes in "virulence or pathogenicity islands". These, according to the author, code for virulence factors (fimbriae) that are known to mediate bacterial attachment to uroepithelial cells to initiate infections pathologically characterised with initiation of events in mucosal epithelial cells that include induction of programmed cell death (apoptosis) and epithelial cell desquamation. Uropathogenic strains of *E. coli* also produce haemolysin and aerobactin (a siderophore for scavenging for iron) and are resistant to the bactericidal action of human serum (Stamm, 2005:1716).

Except in the first year of life according to Russo (2005:881) UTI is uncommon in males in the absence of predisposing infection risk factors e.g. history of instrumentation or anal intercourse. The condition is characterised with dysuria, frequency, and suprapubic pain. Fever and back pain suggests progression to pyelonephritis and pregnant women are more prone to developing this. Prostatic infection is generally a complication of UTI in men with a history of instrumentation and/or prostatic hypertrophy..

- **Abdominal and Pelvic infection**

The abdomen or pelvis is the second most frequent site of extraintestinal infection due to *E. coli* (Russo, 2005:881) with infections of the pathogen at these sites often resulting from a perforated viscus (e.g., appendix, diverticulum) or associated with intra-abdominal abscess, cholecystitis and ascending cholangitis (Madappa & Go, 2009:1). Clinical syndromes occurring in this location are varied and include, peritonitis secondary to faecal contamination, spontaneous bacterial peritonitis, peritoneal dialysis associated peritonitis, diverticulitis, appendicitis, intraperitoneal or visceral abscesses (Russo, 2005:881). In these infections *E. coli* may be isolated alone or in combination with other facultative and /or anaerobic members of the intestinal flora.

- **Pneumonia**

E. coli is not usually considered a cause of pneumonia and enteric gram-negative bacteria in general accounts for only 0% – 9% of cases of community acquired pneumonia according to Arancibia *et al.* (2002:1849). The reason for this, Russo (2005:881) explained, is because these organisms only transiently colonise the oropharynx. Rates of oral colonisation with *E. coli* by the author's indication, however, do

increase with severity of illness and with antibiotic use and under such a condition the organism may assume importance as a cause of pneumonia among patients with long-term-care institutions. The pathogens indeed, and according to Russo (2005:881) accounts for 60 – 70% of cases of hospital acquired pneumonia and is for this reason regarded as the most frequent cause of pneumonia acquired at the hospital. Pneumonia due to enteric GNB is a serious disease with very adverse prognostic potential (Arancibia *et al.*, 2002:1849).

° **Meningitis**

E. coli, the K1 capsular serotype being the most responsible, is one of the two leading causes of neonatal meningitis, the other being *S agalactiae* (Group B streptococci) (Madappa & Go, 2009:1; Russo, 2005: 881). *E coli* meningitis is rare in adults but may occur following neurosurgical trauma or procedures resulting in disruption of the meninges. Seeding of the meninges by the organisms in these instances according to Russo (2005: 881) may presumably come from poorly cleared portal source episodes of bacteraemia or through direct extension from an otogenic or sinus source.

° **Cellulitis/musculoskeletal infection**

E. coli contributes frequently to polymicrobial infections of decubitus ulcers in diabetic patients or other hosts with neuro-vascular compromise (Russo, 2005: 881). According to the author, the pathogen also occasionally causes cellulitis or burns site or surgical wound infections, particularly when the infection originates close to the perineum. It may also a cause of septic arthritis, sinusitis and osteomyelitis (Madappa & Go, 2009:1) *E. coli* also occasionally causes orthopaedic device associated infections or haematogenously acquired myositis (Russo, 2005: 881).

° **Bacteraemia**

E. coli and *S. aureus* are the most common clinically significant bacteria isolates from blood. The former, with a 17% to 37% rate of isolation from bacteraemic blood, is the GNB often isolated from the blood in ambulatory and long term care or hospital settings (Russo, 2005:882; Banister *et al.*, 2000: 364). The urinary tract is the most common source of *E. coli* bacteraemia according to Russo (2005:882) and is most common in pyelonephritis, urinary tract obstruction or instrumentation in the presence of urine. The infection can, however, arise, as the author further indicated, from primary infection at any extraintestinal site or from percutaneous intravascular devices.

- ***Escherichia coli* antibiotic susceptibility**

E. coli is commonly resistant to penicillin and ampicillin by production of β-lactamase (Elliot *et al.*, 2004:53). This precludes the use of these antibiotics in the treatment of *E. coli* associated infections even in community acquired infections (Russo, 2005:882). With current ranges of 10% – 40%, rates of resistance of *E. coli* to 1st generation cephalosporins and co-trimoxazole have been reported to be increasing in the community in the United States (Russo, 2005:882). Ronald (2002:15) reporting from results of a 5-year study (1992 – 1996) that investigated antimicrobial susceptibility patterns in the United States cited significant observed increases in the prevalence patterns of resistance of *E. coli* to co-trimoxazole (from 9% to18%) cephalothin (from 20% to 28%) and ampicillin (from 20% to 34%). According to the author, reports from Europe and the developing countries even demonstrated higher rates of increases in resistance to these antibiotics.

Rates of resistance to 2nd and 3rd generation cephalosporins, quinolones, monobactams (e.g. azthreonam) carbapenems (e.g. imipenem) and the aminoglycosides are generally low in the range of less than 10% (Russo, 2005:882). Significant resistance (30% – 40%) to amoxicillin/clavulanate and piperacillin has also been reported in the United States (Russo, 2005:882). In the 5-year study reported by Ronald (2002:15) resistance to nitrofurantoin and ciprofloxacin among *E. coli* was observed to remain at less than 1%.

- **Antibiotic therapy in *Escherichia coli* infections**

Antibiotics used to treat *E. coli* infections include the **cephalosporins**, **trimethoprim** or its combination with **sulphamethoxazole (co-trimoxazole)**, and **aminoglycosides** (Elliot *et al.*, 2004:53). For urinary tract infections, agents that concentrate in the urine are recommended antibiotics of choice and include **nitrofurantoin, trimethoprim, cephalexin, or amoxicillin/clavulanic acid (co-amoxiclav)** (Bannister *et al.*, 2000: 221).

For specific types of UTIs, the treatment regimens in Table 2.6 which considers as well the likely presence of other mitigating circumstances or possible uropathogens as aetiological agents, are recommended by Stamm (2005: 1719).

Table 2.6: Treatment regimens for bacterial urinary tract infections (Adapted from Stamm 2005:1719)

Condition	**Characteristic pathogens**	**Mitigating circumstances**	**Recommended Antibiotics**
Acute uncomplicated cystitis in women	*E. coli, S. saprophyticus, P. mirabilis, K. pneumoniae*	None	Co-trimoxazole or Trimethoprim or Quinolone (3- day regimen); Nitrofurantoin (7-day regimen)
		Diabetes, symptoms for >7 days, recent UTI, use of diaphragm, age > 65 yrs,	Co-trimoxazole or Trimethoprim or Quinolone (7- day regimen)
		Pregnancy	7-day regimens of Amoxicillin, Nitrofurantoin, cefpodoxime or co-trimoxazole
Acute uncomplicated pyelonephritis in women	*E. coli, S. saprophyticus, P. mirabilis,*	Mild to moderate illness , no nausea or vomiting: out patient therapy	Oral quinolone for 7 – 14 days or Ceftriaxone 1 g (single dose) or Gentamicin (3 – 5 mg/kg)IV followed by oral TMP-SMX for 14 days
		Severe illness or possible urosepsis: hospitalisation required	Parenteral quinolone, gentamicin (+/- ampicillin), Ceftriaxone or aztreonam until defervescence; then oral quinolone, cephalosporin or co-trimoxazole for 14 days
Complicated UTI in men and women	*E. coli, Proteus, Klebsiella, Pseudomonas, Serratia, Enterococci, Staphylococci*	Mild to moderate illness, no nausea or vomiting: out patient therapy.	Oral Quinolone for 10 – 14 days
		Severe illness or possible urosepsis: hospitalisation required	Parenteral Ampicillin + Gentamicin, Ceftriaxone, Aztreonam, Ticarcillin/clavulanate or Imipenem-cilastin until defervescence; then oral Quinolone, cephalosporin or co-trimoxazole for 10 - 21 days

2.1.5.2.2 *Klebsiella* spp

Klebsiella contains a number of species including *K. pneumoniae*, *K. rhinoscleromatis, K. ozaenae* and *K. aerogenes*. *K. pneumoniae* among these is considered the most clinically important member of the group responsible for community acquired, long term care and nosocomial infections.. *K. rhinoscleromatis, K. ozaenae* are associated with infections in tropical climates The pathogens are widespread in the environment and in the intestinal flora of man and other mammals. The majority of their infections occur in long term care facilities and hospitals (Elliot *et al.*, 2004: 53, Russo, 2005:882).

- ***Klebsiella* pathogenesis**

Klebsiella pathogenicity is associated with capsule production (Elliot *et al.*, 2004: 53). Most clinical isolates of *K. pneumoniae* according to Tsay *et al.* (2002:1021) possess a well defined polysaccharide capsule that appears to be a critical virulence factor. Chhibber *et al.* (2003:699) investigated the role of K- and O- capsular lipopolysaccharides of *Klebsiella pneumoniae* in causing lung infections and established that without the capsular lipopolysaccharides the pathogen cannot establish itself in the lung to cause serious infection. They concluded from their study that apart from capsular polysaccharide, the lipopolysaccharide antigen is an important factor in pathogenesis of *K. pneumoniae* in acute respiratory tract infection.

- ***Klebsiella* associated infections and their clinical presentations**

Klebsiella infections are often opportunistic and are associated with hospitalisation. (Elliot *et al.*, 2004: 53; Umeh & Berkowitz, 2009:1). Spectra of infections generally caused by the organisms are similar to those of *E. coli* but with lower incidences of extraintestinal infections at all sites except in the respiratory tract. They include notably pneumonia, urinary tract, abdominal, surgical site and wound infections and also neonatal meningitis and bacteraemia (Russo, 2005:882).

- **Upper respiratory tract infections.**

Klebsiella spp is associated with infections of the upper respiratory tract including nosocomial sinusitis (Russo, 2005:882). *K. rhinoscleromatis* and *K. ozaenae* by indications of the author are respective causative agents for rhinoscleroma and chronic

atrophic rhinitis., Rhinoscleroma is a progressive mucosal layer upper respiratory infection that causes necrosis, and occasional obstruction of the nasal passages (Umeh & Berkowitz, 2009:1).

- **Pneumonia**

K. pneumoniae causes only a small proportion of community acquired pneumonia (Russo, 2005:882.), Umeh and Berkowitz (2009:1) described them as opportunistic pathogens that cause infections, mainly in the middle aged and older patient populations with debilitating diseases such as alcoholism, diabetics and chronic bronchopulmonary disease. The organisms in these instances as they explained gain access into the lungs after the host aspirates colonizing oropharyngeal microbes into the lower respiratory tract. The organisms typically cause necrosis, inflammation, and haemorrhage of the lung tissue and produce thick, bloody, mucoid sputum described as currant jelly sputum (Umeh & Berkowitz, (2009:1). Purulent sputum production and pneumothorax on X-ray are typical of *K. pneumoniae* associated pneumonia as in the case of all pneumonias due to enteric GNB with pulmonary necrosis, pleural effusion, and empyema occurring with disease progression (Russo, 2005:882). Mechanical ventilation is an important risk factor for *K. pneumoniae* lower respiratory tract infections according to Russo (2005:882).

- **Abdominal infections**

Spectrum of abdominal infections caused by *Klebsiella* is the same as that of *E. coli*, though less frequently isolated from these infections than the latter (Russo, 2005:882)

- **Urinary tract infections**.

Except for complicated UTI infections like those associated with indwelling catheters, which may be between 5 to 17%, incidences of *K. pneumoniae* associated UTI in adults are generally low at about only 1 – 2% (Russo, 2005:882).

- **Cellulitis and soft tissue infections**

Klebsiella cellulitis and soft tissue infections occur most frequently in devitalised tissues e.g. decubitus ulcers, diabetes or burn sites and also in immunocompromised hosts. The pathogens may also be significant as aetiological agents for surgical wound infections, osteomyelitis contiguous to soft tissue infections and myositis in minority of cases (Russo, 2005:882).

° **Meningitis**

Klebsiella, is implicated in neonatal meningitis or meningitis associated with neurosurgery (Russo, 2005:882).

♦ ***Klebsiella* antibiotic susceptibility**

The antimicrobial resistance of GNB including *Klebsiella* is variable and is influenced by both geographic location and regional antibiotic use (Russo, 2005:880). *Klebsiella* often produce β-lactamase and are intrinsically resistant to ampicillin and ticarcillin (Elliot *et al.*, 2004:53). Like *E. coli* and to some extent other GNB, *Klebsiella*, demonstrate great propensity to developing multidrug-resistant strains through transfer of plasmid containing genes encoding for extended-spectrum β-lactamases (ESBLs) (Russo, 2005:880; Umeh & Berkowitz, 2009:1). Currently, increasing resistance to 3rd generation cephalosporins (TGCs) is attributed to plasmids with genes encoding for ESBLs which also have been linked with resistance determinants for aminoglycosides, tetracycline and co-trimoxazole (Russo, 2005:880). The author further indicated that up to about 50% ESBL containing strains of the pathogen have also displayed associated resistance to fluoroquinolones. ESBL containing strains are highly virulent. They show capsular type K55, and have an extraordinary ability to spread (Umeh & Berkowitz, 2009:1).

Studying susceptibility of *Klebsiella pneumoniae* isolates from blood specimens of bacteraemic children with febrile neutropenia to the cephalosporins (ceftazidime), carbapenems (imipenem) and the aminoglycosides (amikacin and gentamicin) in a University Hospital in Kuala Lumpur, Ariffin *et al.* (1999:24) reported that *Klebsiella pneumoniae* isolates studied showed resistance rates of 51.6% to ceftazidime, 54.4% to amikacin, 9.5% to gentamicin, and 13% to ciprofloxacin. The isolates according to their findings were 100% sensitive to imipenem. The researchers also reproduced a table in their report, which showed an increase in resistance of *K. pneumoniae* from reported rates of 26% and 21% respectively for ceftazidime and amikacin in 1990 to 52% and 54% in 1997 for the two antibiotics. The two antibiotics according to their report were the antibiotics empirically prescribed for the treatment of *K. pneumoniae* bacteraemia at the oncology unit of the hospital from which the specimens were collected.

Makedou *et al.* (2005:246) in another study they conducted at the AHEPA University Hospital in Thesaloniki, Greece reported *K. pneumoniae* showing no resistance to imipenem in contrast to high resistance rates of most antibiotics they studied including

amikacin, tobramycin, ceftazidime and ticarcillin/clavulanate and piperacillin/tazobactam. Their report also took note of a significant increase in resistance of the pathogen to amikacin from a low resistance rate of 10% in 2000 to a high rate of 50% in 2002. They also recorded the same upward trend in changes in resistance of the organism to ticarcillin/clavulanate and piperacillin/tazobactam, which increased from 75% and 65% in 2000 to 95% and 90% in 2002 respectively.

The influence by both geographic location and regional antibiotic use on the susceptibility of *Klebsiella* to antimicrobials as a cause of the variable reports on sensitivity patterns of the pathogen is shown by reports of Daza *et al.* (2001:213) on their study of antibiotic susceptibility of bacterial strains isolated from patients with community-acquired urinary tract infections in San Cecilio University Hospital in Spain. Their report showed *Klebsiella* isolates they tested exhibiting 100% susceptibilities to cefepime, cefotaxime, ciprofloxacin, amikacin and imipenem which conflicts those of Makedou *et al.* (2005:246) and Ariffin *et al.*(1999:24) who, on the contrary, reported high resistance rates of *Klebsiella* to the aminoglycosides and 3rd generation cephalosporins. All three working groups, however, reported high resistant rates of *Klebsiella* to β-lactam antibiotic combinations with β-lactamase inhibitors and 100% sensitivities to the imipenem. The high rate of resistance of the organisms to the β-lactam antibiotic combinations with β-lactamase inhibitors is an indication that mechanisms other than β-lactamase production, probably alterations in amino acid sequences of penicillin binding proteins in the bacterial membranes might be contributing the organisms' development of resistance to the penicillins.

The author Russo (2005:883), though sounding a note of caution about the possible increase in resistance rates, indicated that currently and generally speaking, *Klebsiella* can be considered as exhibiting resistances of less than 10% to the quinolones, 4th generation cephalosporins (e.g. cefepime), cephamycins (e.g. cefoxitin) and amikacin. Carbapenems e.g. Imipenem according to the author are currently the most active antibiotic against *Klebsiella*.

- **Antibiotic therapy in *Klebsiella* infections**

Cephalosporins, **β-lactamase stable penicillins** and a**minoglycosides** are commonly used to treat *Klebsiella* infections (Elliot *et al.*, 2004:53). However, owing to the variability

in antibiotic resistance of GNB and the influence of geographic locations and regional antibiotic use on the pattern, antibiotic selection for the treatment of *Klebsiella* infections should necessarily be based on local susceptibility patterns (Russo, 2005:880).

.

2.1.5.2.3 *Proteus* spp

Proteus spp are motile, non-lactose fermenting and strongly urease positive GNB that produce pale colonies on MacConkey's agar (Inglis, 2003:249, Elliot *et al.,* 2004:56). They are part of colonic flora of a variety of mammals, birds, fish and reptiles. Clinically important members of the group include *P. mirabilis,* which causes 90% of *Proteus* infections occurring in the community, long term care facilities and hospitals and *P. vulgaris* and *P. penneri* which are isolated from infections contracted in long term care facilities or hospitals (Russo, 2005:883)

- ***Proteus* pathogenesis**

Important virulence factors of *Proteus* include adhesins, flagella, IgA, protease and urease. Urease production enables the organism to hydrolyse urea with the production of ammonia and subsequent alkalinization of the urine. Urine alkalinization leads to precipitation of organic and inorganic compounds with a resultant formation of biofilms on catheters and kidney stones with which the pathogens are highly associated. *Proteus* also generate histamine from contaminated fish and are by this means implicated in the pathogenesis of fish poisoning. *P. mirabilis* colonises healthy individuals but *P. vulgaris* and *P. penneri* are primarily associated with patients with an underlying disease (Russo, 2005:883).

- ***Proteus* associated infections and their clinical presentations**

P. mirabilis causes 90% of *Proteus* infections occurring in the community, long-term-care facilities and hospitals (Struble *et al.*, 2009:1). *P. vulgaris* and *P. penneri* are, on the other hand, associated mainly with infections contracted in long-term-care facilities and hospital (Struble *et al.*, 2009:1; Russo, 2005:883).

- **Urinary tract Infections**

The urinary tract is an overwhelmingly favoured site of *Proteus* infection, though they are seen to cause only 1-2% of cases of UTI in healthy women and only up to 5% of hospital

acquired UTI. The pathogens are responsible, however, for 10 to 15% of complicated UTI, particularly UTI associated with long term catheterization in which their prevalence could be as high as 45% (Russo, 2005:883; Inglis, 2003:249; Struble *et al.*, 2009:1). *Proteus* associated complicated UTI could result in the formation of renal calculi (nephrolithiasis) leading to renal obstruction and renal failure (Russo, 2005:883; Struble *et al.*, 2009:1). Patients may present with urethritis, cystitis, prostatitis, or pyelonephritis. Chronic, recurring stones may be an indication of chronic infection (Struble *et al.*, 2009:1).

° **Other infections**

A variety of hospital acquired or long-term-care associated infections can be caused by *Proteus* (Inglis, 2003:249). Very common among these are pneumonia, nosocomial sinusitis, intraabdominal abscess, biliary tract infections, surgical site infection, soft tissue infection (especially decubitus and diabetic ulcers, osteomyelitis. The pathogens are also causative agents for neonatal meningitis often complicated with cerebral abscess (Russo, 2005: 883).

♦ ***Proteus* antibiotic susceptibility**

Except for tetracycline *P. mirabilis* is considered susceptible to most antibiotics including ampicillin and cephalosporins (Inglis, 2003:249). From 10% to 50% of strains of the pathogens may, according to Russo (2005: 883), and as noted by Luzzaro *et al.* (2001:131), develop acquired resistance to ampicillin and the first generation cephalosporins as isolation rates of strains of extended spectrum β-lactamase (ESBL) producing forms of the pathogen continue to increase. Luzzaro *et al.* (2001:131) noted increasing resistances of *P. mirabilis* to ampicillin and the cephalosporins when they investigated properties of multidrug-resistant, ESBL-producing strains of isolates of the pathogens in a medical microbiology laboratory in Italy. Apart from their reported increase in isolation rates of ESBL-producing *Proteus mirabilis,* the researchers also reported associated with the pathogen, characteristic resistance of the ESBL-producing strains to 3rd and 4th generation cephalosporins and piperacillin which was abolished by tazobactam. The strains also demonstrated multiple antibiotic resistances to a range of antibiotics that included gentamicin, fluoroquinolones and co-trimoxazole. They reported these finding amidst observed therapeutic failures and lack of eradication of ESBL-positive *P. mirabilis* by 3rd generation cephalosporins at their institution and elsewhere.

P. vulgaris and *P. penneri* are more resistant to antibiotics than *P. mirabilis* and generally have intrinsic resistance to ampicillin and the first generation cephalosporins (Inglis, 2003:249). Fourth generation cephalosporins (e.g. cefepime), imipenem, aminoglycosides, co-trimoxazole and the quinolones have excellent activity (up to 90-100%) against *Proteus* infections (Russo, 2005: 883).

- **Antibiotic therapy in *Proteus* infections**

Aminoglycosides, **co-trimoxazole**, **quinolones**, **imipenem** and the **fourth generations cephalosporins** are antibiotics of choice in the treatment of *Proteus* infections (Russo, 2005:883) Inglis (2003:249) also recommended **ampicillin** and the **cephalosporins** as antibiotics of choice in treating *Proteus* infections on the basis of both *P. mirabilis* being usually sensitive to these antibiotics and its being the most common of the *Proteus* species,

2.1.5.2.4 *Salmonella* spp

- **Classifications, morphological characteristics and epidemiology**

There are basically three types of species of *Salmonella*. These include S. *typhi, S. choleraesuis and S. enteritidis* with a large number of serotypes of which more than 2000, mainly of *S. enteritidis*, have been distinguished (Inglis, 2003:249). They are all motile by peritrichous flagella except *S. gallinarium-pallorum* and generally non-lactose fermenting (only 1% ferment lactose) (Lesser & Miller, 2005:897). They are also characteristically urease negative and except for *S typhi*, produce hydrogen sulphide. *Salmonella* species are further divided into serovars based on their possession of major antigenic determinants, which include the somatic O antigens [lipopolysaccharide (LPS) cell wall component] the flagellar H antigens and the surface antiphagocytic Vi antigen restricted only to *S. typhi* and *S. paratyphi* (Inglis, 2003:249; Lesser & Miller, 2005:897).

All serotypes of the species are adapted to grow in both humans and animals and can cause a wide spectrum of diseases. The growth of *S. typhi* and S. *paratyphi* is restricted to man in whom they cause enteric fever. The remainder of the serotypes of the organism referred to as nontyphoidal *Salmonella* can colonise the gastrointestinal tract

of a large number of animals including mammals, birds, reptiles and insects. More than 200 serotypes of non typhoidal *Salmonella* are pathogenic and cause gastroenteritis and other localised infections or bacteraemia in humans (Lesser & Miller, 2005:897).

- ***Salmonella* pathogenesis**

All *Salmonella* infections begin by ingestion of the organism in food or water and a varying inoculum of about 10^3-10^6 colony forming units are needed for disease initiation. A powerful component of host defence mechanism resisting *Salmonella* infection is low pH of the stomach coupled with an intact intestinal integrity. Accordingly, conditions that predispose to decrease stomach acidity e.g. an age of less than 1 year, antacid ingestion or achlorhydric disease or conditions that decrease intestinal integrity e.g. inflammatory bowel disease, history of gastrointestinal surgery or alteration of the intestinal flora by antibiotic increase susceptibility to Salmonella infection (Lesser & Miller, 2005:897; Bannister *et al.*, 2000:171). As Lesser & Miller (2005:897) further indicated, *Salmonella* surviving other host mechanisms including inactivation by bile salts, lysosomes, complement and cationic antimicrobial peptides and reaching the small intestines penetrate the mucous layer of the gut and cross the intestinal layer through phagocytic microfold cells that reside within Peyer's patches. Salmonella proteins reaching the cytoplasm of epithelial cells according to the authors, trigger a process of bacteria-mediated endocytosis. The process starts by a ruffling of the epithelial membranes induced by Vi virulence antigen, a polysaccharide appearing to be essential for *S. typhi* virulence (Bannister *et al.*, 2000:170; Elliot *et al.,* 2004:54). The ruffled epithelial membranes reach out and enclose adherent bacteria within large vesicles. This ultimately results in the transport of the bacteria across the epithelial layer and their subsequent internalisation by the macrophages (Lesser & Miller, 2005:897;.

Bacteria phagocytosed by macrophages are protected from other host defence mechanisms mediated through, for example, polymorphonuclear leukocyte activities, complement system and acquired immune response mechanisms involving antibodies (Lesser & Miller, 2005:898). By the authors' further indications, they also survive the antimicrobial environment of the phagocytes through induced changes in their signal regulatory systems to result, for example, in alterations in bacterial protein expressions necessary to enable them to survive microbicidal activities of the host cell. Modifications

in bacterial outer lipopolysaccharides pursuant to such changes in bacterial protein expressions protect internalised bacteria against microbicidal host cell activities.

Phagocytosed salmonellae (*S. typhi* and *S. paratyphi*) disseminate through out the body in macrophages via the lymphatics and colonise reticuloendothelial tissues e.g. liver, spleen, lymph nodes and bone marrow (Lesser & Miller, 2005:898). According to the authors, secretion of cytokines by macrophages when a critical number of organisms have replicated accounts for the signs and symptoms (fever and abdominal pain) associated with the infection. Hepatosplenomegaly that accompanies *S typhi* infection they further noted is related to the recruitment of mononuclear cells and the development of cell mediated immunity.

Nontyphoidal *Salmonella* infection is characterised by massive infiltration of polymorphonuclear cells into both the large and small bowels. This causes damage to the intestinal mucosa and results in the inflammatory diarrhoea observed with nontyphoidal gastroenteritis (Lesser & Miller, 2005:898).

- **Salmonella associated infections and their clinical presentations**

- **Enteric (typhoid) fever**

Typhoid (enteric) fever is a systemic disease characterised by fever and abdominal pain caused by dissemination of *S. typhi* and *S. paratyphi* (Lesser & Miller, 2005:898). According to the authors and Banister *et al.* (2000:437) the most prominent symptom of the infection is prolonged fever, which may be preceded by non-specific prodrome features as chills, headache, anorexia, cough, weakness, sore throat, dizziness and muscle pains. Gastrointestinal symptoms which are quite variable may demonstrate as either diarrhoea or constipation. Indications of Lesser & Miller, 2005:899 noted that diarrhoea more commonly presents in AIDS patients and children less than 1 year than other patient groups and that about 20% – 40% of patients may present with abdominal pain. Some physical findings including rash located primarily on the trunk and chest, hepatomegaly, epistaxis and bradycardia may also show up early during the disease (Lesser & Miller, 2005: 899). Central nervous system associated symptoms presenting as confusion, bad dreams, frank delirium or even psychosis may occur (Banister *et al.*, 2000:437). Most common complications setting in if left untreated as noted by Banister *et al.* (2000:437) include intestinal bleeding or perforation.

- **Nontyphoidal *Salmonella* infections**

° **Gastroenteritis**

Ingestion of nontyphoidal Salmonella results in gastroenteritis similar to that due to other bacterial or viral pathogens. Nausea vomiting and diarrhoea occur in 6 – 48 hours after the ingestion of contaminated food or water. Patients experience abdominal cramping and fever with loose, generally non-bloody, diarrhoea of moderate stool volume. Diarrhoea is usually self limiting and resolves within 3 – 7 days. Fever also resolves within 72 hours but stool culture may remain positive for 4 to 5 weeks after infection (Lesser & Miller, 2005:901).

° ***Salmonella* bacteraemia and Localised infections**

Salmonella bacteraemia and metastatic infection are uncommon (Bannister *et al.*, 2000:171). Generally, up to 5% of patients with nontyphoidal Salmonella gastroenteritis, and as indicated by (Lesser & Miller, 2005:901), have positive blood cultures and 5% - 10% of such patients may develop localised infections. The condition the authors, however, indicated most commonly develops in infants, the elderly and patients with underlying infection or immunosuppression.

Localised infections for which nontyphoidal *Salmonella* could be aetiological agents include intraabdominal infections, which are rare; meningitis which usually is seen in neonates less than 4 months; pulmonary infections presenting as lobar pneumonia sometimes complicated by lung abscesses, empyemas, pleural effusions and bronchopleural fistulas; urinary and genital tract infections presenting as cystitis or pyelonephritis usually in association with malignancy, urolithiasis, structural abnormalities or immunosuppression. Genital infections are rare and present as ovarian and testicular abscesses, prostatitis or epididymitis (Lesser & Miller, 2005:901). Sites of tissue damage most commonly involving bones and joints including those of sickle cell sufferers and arterial aneurysms may become infected by salmonellae (Bannister *et al.*, 2000:171).

- ***Salmonella* antibiotic susceptibility**

According to Lesser and Miller (2005:901), *Salmonella* was first noticed to develop plasmid mediated resistance to chloramphenicol in 1970. Until then, the drug had been the antibiotic of choice in treating *S. typhi* infections or what is referred to as typhoid

fever. In 1989, as the authors further stated, multi drug resistant strains of this serotype of the species emerged and were found to be resistant to chloramphenicol, ampicillin, trimethoprim, streptomycin, sulphonamides and tetracycline and by 1994 12% of all isolates of *S. typhi* in the United States were multi drug resistant. The aminoglycosides and the 1st and 2nd generation cephalosporins demonstrate excellent in vitro activity towards *Salmonella* but are ineffective in treating clinical infections of the pathogens. The quinolones are most likely to be active against salmonellae (Bannister *et al.*, 2000:173) though, resistance to this class of antibiotics has also been seen to be emerging, with an observed outbreak in Vietnam in 1993 of nalidixic acid resistance strains of *S. typhi* infection, which was linked to chromosomal mutations of the gene encoding DNA gyrase, the target point of action of the quinolones (Lesser & Miller, 2005:900).

Mills-Robertson *et al.*, (2002:249) examined clinical isolates of *S. typhi* in Ghana for their susceptibility to ampicillin, chloramphenicol, streptomycin, tetracycline and co-trimoxazole and reported 8.6% resistance of the isolates tested to all five antibiotics, 17.2% to ampicillin, chloramphenicol, and co-trimoxazole, the supposedly first line antibiotics for the treatment of typhoid fever. Fifty nine percent (59.6%) of all isolates by their findings were resistant to at least one of the antibiotics used in the investigation. Additionally, the researchers reported that 24.1% of the 58 strains of the isolates they tested contained plasmids that were transformable and that 42.8% of such plasmids encoded for multiple drug resistance. They concluded from their findings that multiple drug resistant strains of *S. typhi* may be more prevalent in Africa than previously thought.

Some other studies as reviewed below also investigated antibiotic susceptibility trends in non-typhoid Salmonella strains or serotypes. Szych *et al.* (2001:38) studied the antibiotic resistance in *Salmonella enterica* sub spp *enterica* strains isolated from stools of patients with diarrhoea in Poland and reported various levels of resistance of these pathogens to a number of antibiotics in use. Specifically, they noted high levels of resistance of the serotypes to tetracycline and streptomycin, to which the strains demonstrated respectively 91.5%and 86.8% resistance. Other resistance levels of the organisms to various antibiotics as the researchers reported were 42.6%, 34%, 26.4% and 21.4% respectively for nalidixic acid, sulphonamides, ampicillin and furazolidone.

Lower resistance levels were recorded and in a declining order for chloramphenicol, kanamycin, co-trimoxazole, and gentamicin.

Investigating susceptibility of non-typhoidal *Salmonella* isolated from children less than 13 years of age who were admitted to a rural district hospital in Kenya with bacteraemia over a time period extending over 1994 to 2005, Kariuki *et al.* (2006:169) established a trend of reduced prevalence of resistance of *Salmonella* to commonly used antimicrobials. Specifically, they found out that these organisms which were composed of the serotypes *Salmonella enterica* serovar Typhimurium and *Salmonella enterica* serovar Enteritidis demonstrated a remarkable decrease in levels of resistance to amoxicillin and co-trimoxazole, from highs of 62.2% and 68.4% during 1994 – 1997 to respective lows of 11% and 13% in 2002 – 2005. The findings of these workers further established that all non-typhoidal Salmonella remained fully susceptible to cefotaxime and ciprofloxacin.

- **Antibiotic therapy in *Salmonella* infections**

Until the emergence of plasmid-mediated resistance to chloramphenicol, this antibiotic remained standard treatment for typhoid fever. Owing to increased mortality associated with chloramphenicol resistance coupled with its rare cases of induction of bone marrow toxicity, **Ampicillin** (1 g orally every 6 hours) and **co-trimoxazole** (one double strength twice daily) have become the mainstays of treatment of the infection (Lesser & Miller, 2005:899). With current trends of salmonella antibiotic susceptibility, Bannister *et al.*, 2000:173 and Lesser & Miller 2005:900, recommended the following antibiotic treatments of choice in enteric fever.

First line:
Ciprofloxacin 500 mg or Ofloxacin 400 mg orally twice daily for 10 days
Ceftriaxone 1 – 2 g IV or IM for 10 – 14
Alternatives:
Co-trimoxazole 960 mg or Trimethoprim 200 mg orally twice daily for 5-7 days

Nalidixic acid resistant strains:
Azithromycin 1 g orally daily for 5 days or
Ciprofloxacin 10 mg/kg orally for 10 days.

According to Lesser & Miller (2005:902), antibiotic treatment is not generally recommended for *Salmonella* gastroenteritis for reasons that the symptoms usually are self limiting and have not been demonstrated to be altered by short causes of antibiotics. In addition, antibiotic treatment of the infections has been associated with increased rates of relapse and prolonged gastrointestinal carriage. In a review on antibiotics for treating salmonella gut infections Sirinavin and Garmer (1999:1) also noted that there doesn't appear to be any evidence of a clinical benefit of antibiotic therapy in other wise healthy children and adults with non-severe salmonella diarrhoea and that antibiotics do appear to increase adverse effects and also tend to prolong salmonella detection in stool. Focal infections or life threatening bacteraemia with non typhoidal Salmonella are treated with same antibiotics at same doses as indicated for enteric fever (Lesser & Miller, 2005:902). Banister *et al.* (2000:173) indicated the need for long courses of treatment to clear salmonella from infected sites.

2.1.5.2.5 *Shigella* spp

Keusch & Kopecko (2005:902) described shigellae as small, non-lactose fermenting and non-motile bacilli. They are related to *E. coli* so closely, as the authors described further, as to be indistinguishable from the latter by DNA hybridization methods. There are four pathogenic species, which are distinguished based on somatic O antigens and biochemical reactions. They include *S. dysenteriae, S. flexneri, S. boydii* and *S. sonnei* (Elliot *et al.,* 2004:55). All shigellae produce acid but not gas from glucose (Keusch & Kopecko, 2005:902). The organisms, the authors further stated, are highly host adapted and are characterised by their ability to invade intestinal epithelial cells and cause infection and illness in humans. They considered, hence, natural pathogens only of humans and higher primates.

- ***Shigella* pathogenesis**

Shigella enters the host through the oral route and readily passes the gastric acid barrier because of its genetic ability to survive low pH. The pathogens causes disease by invasion and destruction of the colonic mucosa (Elliot *et al.*, 2004: 55). Their ability to evade cells after their initial attachment to the colonic epithelium involves a process in which the pathogens induce their own uptake through a host endocytic mechanism, a phagocytosis-like type of process in which the bacteria are initially engulfed within

plasma membrane (enclosed endosomes) and later released into the nutrient rich cytoplasm when the bacteria dissolve the endosomal vacuole (Keusch & Kopecko, 2005:903). The intracellular environment provides a means of the bacteria's evasion of host defence mechanisms. The bacteria replicate in the cytoplasm and get attached to the plasma membrane where they form protrusions at the interface between adjacent cells. Pinching off of the protrusions results in the lysis of the double host cell membrane surrounding the organism, and it's passing on into the cytoplasm of the new cell. The process of replication in the new cell and the formation of protrusions are repeated and result in a progressive cell to cell spread of the organism without a re-exposure to extracellular environment and host immune defences after its initial entry into a host cell (Keusch & Kopecko, 2005: 904).

Invading shigellae invoke the production of the chemokine interleukin-8 (IL-8) by the host colonic epithelial cells. IL-8 induces migration of PMNs through the epithelial layer into the intestinal lumen. The epithelial tight junctions become damaged as the PMNs traverse the mucosa and allows for further *Shigella* invasion and exacerbation of inflammation. The consequences are mucosal ulcerations and characteristic dysenteric small volume stools consisting of mucus, cellular debris, neutrophil exudates and blood. (Keusch & Kopecko, 2005:903).

Apart from its ability to directly invade cells *Shigella* also produces enterotoxins that promote virulence of the pathogens. *S. dysenteriae* produces Shiga toxin, related members of which are also produced by Shiga toxin-producing *E. coli* (STEC) (Unkmeir & Schmidt, 2000:4861; Keusch & Kopecko, 2005:904). Shiga toxins according to Keusch & Kopecko (2005:904) are associated with haemorrhagic colitis and haemolytic uraemic syndrome. They target endothelial cells and seem to play a role in the pathogenesis of microangiopathic complications associated with toxin producing shigellae and *E. coli*. Two other enterotoxins, ShET-1 and ShET-2 have also been described for shigellae. ShET-1 is exclusively produced by *S. flexneri* while ShET-2 is more widely distributed among the species and strains of intestinal pathogenic *E. coli* e.g. enteroinvasive *E. coli*. The two enterotoxins induce electrolyte imbalance in the gastrointestinal tract and may be involved in the pathogenesis of watery diarrhoea phase of shigellosis (Keusch & Kopecko, 2005:904).

- ***Shigella* associated infections and their clinical presentations**

Shigella infection causes dysentery, a disease characterised by frequent passage of small volume stools consisting of blood, mucus and pus and accompanied by severe abdominal cramps and tenesmus (Elliot *et al.,* 2004:55; Keusch & Kopecko, 2005:904). The infection is usually limited to the colon with other extraintestinal complications like septicaemia or meningitis showing up as extremely rare events (Inglis, 2003:249; Keusch & Kopecko, 2005:904). Majority of extraintestinal complications of shigellosis that occur arise in patients in developing countries and are related to prevalence of infections caused by *S dysenteriae* type 1 and *S flexneri*. Haemolytic uraemic syndrome manifesting from the effects of Shiga toxin may occur with infections with *S. dysenteriae* type 1 with which the enterotoxin production is associated (Keusch & Kopecko, 2005:904; Baninister *et al.*, 2000:174).

- ***Shigella* antibiotic susceptibility**

Resistance of *Shigella* to sulphonamides, streptomycin, chloramphenicol, and tetracyclines is almost universal (Keusch & Kopecko, 2005:905). Many strains of the organisms by the authors' note are also now resistant to ampicillin and co-trimoxazole particularly in the developing countries where resistance to these antibiotics is commonplace. Antibiotic susceptibility testing of *Shigella* spp isolated from stool specimens in Dakar and identified by the National Senegalese Enterobacteriaceae Center was carried out by Dromigny *et al.* (2004:109) between 2000 and 2004. Their reported findings showed an alarming increase in resistance of the pathogens, particularly among *S. flexneri* isolates which they identified as the major cause of shigellosis in Dakar, to the antibiotics tested. The report did not provide percentage resistance or sensitivity or percentage resistance increase figures of the pathogen to the antibiotics but did mention that the results confirmed earlier percentage increase figures between the early 1980s and 1990s which were recorded as 10% – 32.3% for ampicillin, 18.4% - 30% for co-trimoxazole and 35% – 76% for tetracycline.

The fluoroquinolones are currently highly effective against all strains of shigellae (Keusch & Kopecko, 2005:905).

- **Antibiotic therapy in *Shigella* infections**

Antibiotic use is recommended in the treatment of severe cases of shigellae infections due to *S. dysenteriae* and *S. flexneri.* Antibiotic of choice in the developing countries are the quinolones e.g. n**alidixic acid** or **ciprofloxacin** (Keusch & Kopecko, 2005:906). Alternative drugs shown to be effective in the treatment of the infections as indicated further by the authors include **pivampicillin**, **azithromycin** and **ceftriaxone.**

On the basis of their physico-chemical properties which reflect in their modes of absorption, the following antibiotics are advised not to be used in treating Shigella infections.

- *Amoxycillin*: Amoxicillin is absorbed in the proximal area of the intestine and is ineffective in treating shigellae infections which are localised in the colonic lumen. The antibiotic for this reason should not be substituted for ampicillin in treating shigella infections (Keusch & Kopecko, 2005:905).
- *Nonabsorbable antibiotics* e.g. *Neomycin*: Antibiotics in this category do not reach the mucosal bacterial population and are similarly not effective, and hence are not to be used, in treating shigellae infections (Keusch & Kopecko, 2005:905).

Antibiotic treatments are not recommended for the convalescent carrier state which is no more than a few weeks. In patients with AIDS however, chronic carriage of *Shigella* can develop and relapsing infections with bacteraemia may ensue. In such patients, the chronic carrier state may be interrupted by several weeks of treatment with quinolones. (Keusch & Kopecko, 2005:906)

2.1.5.2.6 *Haemophilus* spp (Parvobacteria)

Haemophilus spp require growth factors present in blood to grow on solid media. Pathologically important members of the genus include *H. influenzae, H. aegyptius, H ducreyi* and *H. parainfluenzae.* They are facultative organisms and are distinguished in part by their differing requirement for factors X (haemin) and V (nicotinamide adenine dinucleotide (NAD) (Inglis, 2003:251).

Haemophilus influenzae is exclusively a human pathogen according to (Murphy, 2005:864). Six major serotypes of it as the author indicated, have been identified and

designated "a" through "f" based on their antigenically distinct polysaccharide capsules. Some strains of the species lack capsules and are referred to as nontypable strains. *H influenzae* type b (Hib) and the nontypable strains are the most relevant strains clinically with Hib causing disease primarily in infants and children under the age of 6 years while the nontypable strains are primarily mucosal pathogens (Murphy, 2005:864).

- ***Haemophilus* pathogenesis**

Strains of *H. influenzae* type b cause systemic disease by invasion and haematogenous spread to distant sites such as the meninges, bones and joints (Murphy, 2005:864). The type b polysaccharide capsule of the organism according to the author, enables it to avoid opsonization and hence phagocytosis and is considered an important virulence factor of the pathogen. Other pathogenicity factors of the pathogens include cell wall lipopolysaccharides, outer membrane proteins, pilus proteins and immunoglobulin A protease (Bannister *et al.*, 2000:273). Antibodies developed against the capsules offer protection against infections of the pathogens and by age 6 years when the child develops enough of these antibodies infections by Hib become unusual. Nontypable *H. influenzae* strains by indications of Murphy (2005:864) cause disease by local invasion of mucosal surfaces mainly. Immune responses to the strains appear to be strain-specific and partly account for the ability of nontypable *H. influenzae* to cause recurrent infections.

- ***Haemophilus* associated infections and their clinical presentations**

H. influenzae type b is mainly associated with childhood infections. It causes, for example, meningitis in infants less than 2 years of age, epiglottitis in older children of 2 – 7 years, cellulitis in young children and pneumonia in infants. Survivors of Hib meningitis very often have some neurologic sequelae such as permanent or partial hearing loss, delay in language development or some significant handicap of some type. Less commonly Hib infection in children may cause such invasive conditions as osteomyelitis, septic arthritis, pericarditis, orbital cellulitis, urinary tract infections, abscesses and bacteraemia. (Murphy, 2005:865)

Nontypable *H influenzae* further to Murphy's (2005:865) notations is a common cause of lower respiratory tract infections in adults, notably pneumonia and exacerbations of chronic obstructive airways disease. The pathogen according to the author is also one of

the three most common causes of childhood otitis media after *S. pneumoniae* and *Moraxella catarrhalis*. Nontypable *H. influenzae* associated otitis media is often preceded by viral infections of the respiratory tract. The pathogen also causes puerperal sepsis and neonatal bacteraemia as well as sinusitis in adults and children.

- ***Haemophilus* antibiotic susceptibility**

Approximately 25% of strains of *Haemophilus influenzae* produce β-lactamase and are resistant to ampicillin (Murphy, 2005:865; Elliot *et al.*, 2004:59). In a study in which Saha *et al.* (2005: 228) determined resistances of invasive *H. influenzae* type b isolated from blood and cerebrospinal fluid specimens of Bangladeshi children with meningitis and pneumonia, resistance rates of 32.5%, 21.5% and 49.2% were reported respectively for the pathogens against ampicillin, chloramphenicol and co-trimoxazole. Jacobs and Dagan (2004: 13) reported a 13% rate of increase in the resistance of *H. influenzae* to co-trimoxazole worldwide. In a Sentinel Project report in Italy, Marchese *et al.* (2005:10) noted that majority of antibiotics tested in that country displayed a remarkable antibacterial activity against *Haemophilus* species. The β-lactam antibiotics cefixime, ceftriaxone (3rd generation cephalosporins) cefaclor, (1st generation cephalosporin) and amoxicillin/clavulanate respectively demonstrated percentage activities of 100%, 100%, 97.9% and 99.9% towards the pathogens. In the category of non β-lactam antibiotics, ciprofloxacin and azithromycin were seen to show activities of 100% each against the organism. Chloramphenicol and tetracycline were 98.8% and 96.3% active against the organisms. Clarithromycin (88.8%), ampicillin (87%) and co-trimoxazole (80.1%) were less effective in comparison with other antibiotics tested.

Inoue *et al.* (2004:47) in their PROTEKT 1999 - 2000 report documented an overall prevalence of β-lactamse production of *H. influenzae* in the Far East as 17.2% with South Korea and Japan showing the highest and lowest respective rates of 64.7% and 8.5%. The report also indicated the identification of a single β-lactamase negative ampicillin resistant strain in Japan. Of the β-lactam antibiotics tested, the researchers reported the 3rd generation oral cephalosporins cefditoren, cefixime and cefpodoxime, with their respective demonstrations of 100%, 100% and 99.5% activities against *H. influenzae*, as the most active antibiotics against the pathogen. Generally, resistance to chloramphenicol (7.5%), tetracycline (10.7%) and co-trimoxazole 9.4%, the report further indicated were low. In South Korea, the country with the highest β-lactamase producing organisms however, the prevalence of resistance rates of these antibiotics were

respectively 29.4%, 33.3% and 41.2%. The observed high rates of resistance in South Korea interpreted against the findings that percentage resistances of the pathogens against the three antibiotics reported for the region were composed of β-lactamase positive organisms which, in the respective cases of chloramphenicol, tetracycline and co-trimoxazole, were 27 out of 28, 33 out of 40 and 23 out of 35 of all resistant isolates (Inoue *et al.,*

2004:47), suggests an association between the development of *Haemophilus* resistance to the three antibiotics to their acquisition of β-lactamases, particularly in the cases of chloramphenicol and tetracycline.

Biofilms, by virtue of their ability to protect organisms enclosed in them from antibiotic killing or change the characteristics of biofilm cells, like reduction in cellular growth rate, are known to confer resistance on microbes to antibiotics (Abdi-Ali *et al.,* 2005:196). Slinger *et al.* (2006:251) indicated that *H. influenzae* has been shown to grow in biofilms on middle ear mucosa. The researchers hypothesized that this form of the pathogens might be the aetiologic agents of otitis media with effusion which generally is unresponsive to antibiotic treatment. Based on this hypothesis, they conducted a study to find out if biofilm isolates become more resistant in the biofilm state and if they did, which antibiotic or combinations of antibiotics could be considered most effective against biofilm cultures. They specifically investigated the susceptibility of nontypable *H. influenzae* isolates grown as planktonic and biofilm cultures to multiple antibiotic combinations. They findings of their study (Slinger *et al.* 2006:251) showed that,

- *H. influenzae* growing as biofilms demonstrate much decreased sensitivity to β-lactam antibiotics in comparison to sensitivities demonstrated by the planktonic grown isolates of the pathogen.
- antibiotic combinations that included rifampicin and ciprofloxacin appeared most effective against *H. influenzae* biofilm isolates and that the effects of these two antibiotics on the biofilm isolates of the pathogens might be additive or synergistic.
- biofilm sensitivity testing exhibited differences among the in vitro effectiveness of antibiotics against biofilm isolates that cannot be predicted from planktonic testing. They found, for example, that though both ciprofloxacin and cefixime were very effective against planktonic grown isolates of the pathogen, only

ciprofloxacin retained its activity against the biofilm isolates. Cefixime, a β-lactam antibiotic demonstrated no activity against biofilm grown isolates of *H. influenzae*

- **Antibiotic therapy in *Haemophilus* infections**

Murphy (2005:865) and Bannister *et al.* (2000:273) suggest for the treatments of *Haemophilus* type b meningitis in children **cefotaxime** 150-200 mg/kg daily in three or four divided doses or **ceftriaxone** 75 – 100 mg/kg in 12 hourly divided doses for 1 to 2 weeks. As alternative treatments the authors suggest **ampicillin** 200 to 300 mg/kg daily in four divided doses plus **chloramphenicol** 75 to 100 mg/kg daily in four divided doses for the same period of treatment. Invasive infections other than meningitis are treated with same antibiotics.

Administration of glucocorticoids to patients with Hib meningitis reduce the neurologic sequelae of the infection and as part of the antibiotic management **dexamethasone** is advised to be given at a dose of 8mg twice daily for the first three days of antibiotic treatment (Murphy, 2005: 865; Bannister *et al.*, 2000: 273).
Infections with nontypable strains of *H. influenzae* may be treated with **ampicillin** and in the event of such infections being caused by ampicillin resistant strains with a variety of agents including **co-trimoxazole**, **amoxicillin/clavulanic acid**, **cephalosporins** and more recent macrolides – **azithromycin** or **clarithromycin**. Fluoroquinolones are highly active against *H. influenzae* but are not recommended for treatment of children or pregnant women because of the possibility their causing articular damage (Murphy, 2005:865)

H. ducreyi chancroid is treated with 1 gm oral single dose of **azithromycin.** For alternative treatments **ceftriaxone** 250 mg IM as a single dose, or **ciprofloxacin**
500 mg twice daily for 3 days or **erythromycin** 500 mg four times daily for 7 days are recommended (Murphy, 2005:867).

2.1.5.2.7 *Pseudomonas aeruginosa*

P. aeruginosa is a commensal of the human gastrointestinal tract capable of colonising other sites when host mechanisms are compromised (Elliot *et al.*, 2004:67). It grows under conditions of minimal nutrient requirement, even in water and in the presence of some disinfectants (SS*t al.*, 2009:1). This property enables it to survive easily in hospital

environments where it serves as an important pathogen in nosocomial infections (Elliot *et al.*, 2004:67). By Elliot *et al.'s* (2004:67) further indications, they are oxidase positive strict aerobes that undergo oxidative metabolism. They grow on most media to produce a characteristic greenish pigment .

- ***Pseudomonas* pathogenesis**

P. aeruginosa is an opportunistic organism that rarely causes infections in healthy individuals (Qurah *et al.*, 2009:1). It is highly virulent in persons in whom normal cutaneous or mucosal barriers have been breached, immunologic defence mechanisms have been compromised, or the protective function of normal bacterial flora has been disrupted (Ohl & Pollack, 2005:889). Both intrinsic and extrinsic factors play roles in *P. aeruginosa* pathogenicity. Its attachment to epithelial cell is facilitated through the use of fimbriae or pili and the elaboration of a mucoid exopolysaccharide which, additional to its facilitation of the organism's attachment to epithelial cells, forms biofilms that protect the infecting cells from humoral and cellular host defence mechanisms as well as inhibiting mucociliary clearance of the organisms. The pathogen also produces enzymes, principally alkaline proteases, elastases and phospholipase C which invariably facilitates the pathogen's tissue invasion through proteolysis of immunoglobulin and complement (alkaline phosphatase), destruction of elastic tissues including lamina of blood vessels (elastases) and the breakdown of lipids and lecithin (phospholipid C) (Ohl & Pollack, 2005:890; Abdi-Ali *et al.*, 2005:196).

Like other gram-negative bacteria *P. aeruginosa* releases lipopolysaccharide endotoxins that are responsible for symptoms of its infection such as fever, leukocytosis or leukopenia, hypotension, shock, disseminated intravascular coagulation, adult respiratory distress and systemic inflammatory response syndromes (Ohl & Pollack, 2005:890).

P. aeruginosa also produces exotoxins that serve as additional virulence factors responsible for the initiation of diseases associated with infections of the pathogen. Notable among these are ExoA, ExoS, ExoT, ExoU and ExoY. Through various mechanisms these exotoxins cause inhibition of host protein synthesis (ExoA), disruption of cellular actin cytoskeleton (ExoS and ExoT), cytotoxicity (ExoU) and

increase in intracellular cAMP (cyclic adenosine monophosphate) (Ohl & Pollack, 2005:890).

- ***Pseudomonas* associated infections and their clinical presentations**

P. aeruginosa is one of the most important opportunistic human pathogens (Abdi-Ali *et al.* 2005:196) It is associated with various infections principally in hospitalised patients, patients with comorbid conditions, patients in whom the immune system is compromised as for example in extremes of age, in diseases such as diabetes mellitus, haematologic malignancies complicated with neutropenia, AIDS and patients with disruption of cutaneous or mucosal barriers (Ohl & Pollack, 2005:892). In these categories of patients, *P. aeruginosa* as may be responsible for the following infections as cited below:

- **Skin and soft tissue infections:** These may present in some patients as *P. aeruginosa* bacteraemia associated ecthyma gangrenosum, pustular lesions, bullae, deep abscesses and cellulitis and also primary *P. aeruginosa* pyoderma which may occur when skin breaks down secondary to surgery, penetrating trauma, burn injury, dermatitis, ulcers related to pressure sores and peripheral vascular disease (Banister *et al.*, 2000:99; Elliot *et al.*, 2004:68; Ohl & Pollack, 2005:892; Qurah *et al.*, 2009:1).

- **Respiratory tract infections:** Pseudomonas associated infections according to Ohl and Pollack (2005:890) often present as primary pneumonia in hospitalised patients who have aspirated secretions of the upper respiratory tract and who may have been on a previous history of antibiotic use or as ventilator associated or bacteraemic pneumonia. This is particularly seen according to the authors and also Qurah *et al.*, 2009:1), in patients with chronic lung disease, congestive cardiac failure, AIDS or neutropenia. Fever, chills, severe dyspnoea, cyanosis, productive cough, apprehension, confusion and other signs of severe systemic toxicity may be characteristically observed while chest X-ray may reveal typically bronchopneumonia with nodular infiltrates and pleural effusions (Ohl & Pollack, 2005:890). Mucoid strains of *P. aeruginosa* with biofilm forming capability exclusively cause chronic lower respiratory infection in older children and young adults with cystic fibrosis or patients with bronchiectasis and AIDS (Bannister *et al.*, 2000:142; Ohl & Pollack, 2005:890).

- **Bacteraemia:** Clinical features of *Pseudomonas* bacteraemia as Ohl and Pollack (2005:890) indicated are similar to those caused by other organisms and commonly include fever, tachypnoea, tachycardia and prostration. Disorientation, confusion or obtundation and other signs of systemic toxicity the authors further noted may be typically present with *P. aeruginosa* bacteraemia while hypotension often associated with the bacteraemia may progress to shock (Ohl & Pollack, 2005:890). Skin lesions for example ecthyma gangrenosum as indicated above may typically present in some patients with *P. aeruginosa* bacteraemia (Qurah *et al.*, 2009:1).

- **Endocarditis** where the pathogen is often seen infecting native heart valves of intravenous drug users or prosthetic valves in patient groups with the devices. All heart valves and the mural endocardium may be involved in *P. aeruginosa* endocarditis (Ohl & Pollack, 2005:891). Cardinal features of bacterial endocarditis according to Qurah *et al.* (2009:1) include fever, murmur, and positive blood culture for the causative. Peripheral stigmata of endocarditis as the authors further indicated include Roth spots, Janeway lesions, Osler nodes, splinter hemorrhages, and splenomegaly.

- **Urinary tract infections (UTI):** *Pseudomonas* UTIs are usually hospital-acquired and are associated with catheterization, instrumentation and surgery (Qurah *et al.*, 2009:1). The infections according to Ohl and Pollack, 2005:892) are also common in patients with urinary tract obstruction arising, for example, from enlarged prostate or renal stones or those who have undergone surgery or on whom instrumentation procedures of some kind have been carried. Clinical features of the infection according to the authors are similar to those of other bacterial infections but they may exhibit propensity for persistence, chronicity and recurrence. Multi-drug resistance strains of *P. aeruginosa* are often implicated in chronic or recurrent nosocomial UTI (Ohl & Pollack, 2005:892).

- **Eye infections:** Eye infections caused by *P. aeruginosa* often present as keratitis (corneal ulcer) with typically progressive inflammation of ocular cavities and their adjacent structures (endophthalmitis). It may result from corneal injuries which interrupt the integrity of the superficial epithelial surface to permit bacterial access to the underlying stroma (Ohl & Pollack, 2005:891). The infection may also present as

keratoconjunctivitis with blurred vision in contact glass wearers (Banister *et al.*, 2000:113)

- **Ear infections:** *P. aeruginosa* is the dominant aetiologic pathogen for otitis externa, a benign inflammatory process affecting the external auditory canal (Ohl & Pollack, 2005:891). The pathogen is also a common cause of chronic otitis media (Qurah *et al.*, 2009:1). In otitis externa according to Ohl & Pollack (2005:891) the infecting organism may occasionally penetrate the epithelium overlying the floor of the external auditory canal to invade the underlying soft tissue and cause what is termed malignant external otitis. It occurs predominantly in elderly diabetic patients (Qurah *et al.*, 2009:1). Otorrhoea and severe otalgia are the typical presenting symptoms (Ohl & Pollack, 2005:891; Qurah *et al.*, 2009:1). Swimmers and divers whose ears are often wet are prone to pseudomonal otitis externa cause by water borne organisms (Banister *et al.*, 2000:100)

- **Central nervous system (CNS) infections**: *Pseudomans* associated CNS infections often present as meningitis or brain abscess (Ohl & Pollack, 2005:891). According to the authors, they may originate as extensions from contiguous parameningeal structures such as the ear, the mastoid or the paranasal sinus or be directly inoculated into the subarachnoid space or brain through head trauma, surgery or diagnostic procedures or they may be results of bacteraemic spread from distant sites. Clinical features of *P. aeruginosa* meningitis are similar to other forms of acute bacterial meningitis and may include fever, headache, stiff neck, confusion and obtundation (Ohl & Pollack, 2005:891).

- **Bone and joint infections:** Bone and joint infections caused by *Pseudomanas* spp according to Ohl and Pollack (2005:892) are exemplified by sternoclavicular pyoarthrosis (*suppuration of sternoclavicular joints*) in which, the patient presents with acute or chronic pain in the anterior chest wall; infections of symphysis pubis (*cartilaginous joints of the pubic bones*) which may be associated with pelvic surgery and injection drug use; vertebral osteomyelitis which may be complications of UTI in the elderly, genitourinary instrumentation, surgery or injection drug use; and osteochondritis of the foot (*inflammation of both bones and cartilage of the foot*), which is an acquired infection of the small joints and bones of the foot seen primarily in children following inoculation of puncture wounds of the plantar or foot

sole by *P. aeruginosa* naturally inhabiting the moist environment found in the soles of shoes

- ***Pseudomonas* antibiotic susceptibility**

Antibiotic resistance in *P. aeruginosa* is both intrinsic and acquired (Ohl & Pollack, 2005:893). Characteristically, the pathogen is resistant to many antibiotics making it necessary for newer antibiotics to be designed to specifically combat the organism (Elliot *et al.*, 2004:68). The organisms with biofilm forming capabilities are particularly difficult to eradicate with antimicrobial treatment and in vitro susceptibility tests show considerable resistance of biofilm cells to killing (Abdi-Ali *et al.*, 2005:196). Currently important anti-pseudomonal antibiotics are considered to include the aminoglycosides, broad spectrum penicillins (e.g. piperacillin), third generation cephalosporins (e.g. ceftazidime) and the quinolones (e.g. ciprofloxacin) (Elliot et al., 2004:68).

A number of studies worldwide investigated susceptibility of these organisms to these so-termed anti-pseudomonas antibiotics. In one such study in Italy, Blandino *et al.* (2004:516) indicated amikacin (an aminoglycoside) among a group of antibiotics investigated as exhibiting the highest activity against *P. aeruginosa.* The pathogens demonstrated a sensitivity incidence of 79.6% to this antibiotic. The carbapenems meropenem and imipenem and the broad spectrum penicillins piperacillin/tazobactam and piperacillin in that order and according to results reported by the researchers, exhibited next higher levels of activities of 77.8%, 73.1%, 73.2% and 72.2% against the pathogen. The third and fourth generation cephalosporins, ceftazidime and cefepime and the fluoroquinolone, ciprofloxacin, showed lower levels of activity against the pathogens. The pathogens demonstrated sensitivity incidences of 64.8%, 59.3% and 45.4% respectively towards these antibiotics. In summary and on the assumption that cross resistances most often exist within drugs of the same class, the results of Blandino *et al.* (2004:516) study can be said to show that the *P. aeruginosa* strains studied were appreciably sensitive to the aminoglycosides, the carbapenems and the anti-pseudomonal penicillins, very moderately sensitivity to the 3rd and 4th generation cephalosporins and a rather resistant to the fluoroquinolones.

Some other studies on *P. aeruginosa* susceptibility patterns as also documented below, tried to establish differences in sensitivities or resistances of the pathogens to anti-

pseudomonal antibiotics within the same class. Japoni *et al.* (2006:344,345) in one such study established a sensitivity pattern of *P. aeruginosa* isolated from burn patients in Iran which showed the organism to be more sensitive to meropenem than imipenem, though the two carbapenems demonstrated the highest activity among the group of antibiotics tested against the organisms. Within the penicillin and β-lactamase inhibitor combination group, piperacillin/tazobactam showed higher anti-pseudomonal activity in comparison with ticarcillin/clavulanate. The two antibacterial agents, however, showed the least anti-pseudomonal activity against the pathogen among the group of antibiotics against which the pathogen was tested. Among the aminoglycoside group, amikacin was shown to exhibit the best activity while in the cephalosporin group ceftazidime was the most active. The researchers (Japoni *et al.,* 2006:344,345) also established the following trends in demonstration of cross resistances of isolates to the different antibiotics.

- All amikacin resistant isolates were resistant to tobramycin and cefepime.
- Majority of amikacin resistant isolates showed cross - resistance to ceftazidime and piperacillin/tazobactam
- Almost all of the resistant isolates of the pathogens showed cross resistance to cefepime
- Majority of imipenem and meropenem resistant isolates demonstrated cross resistance to the rest of the antibiotics

In another study in which Makedou *et al.* (2005:246) investigated changes in resistances of most common gram-negative bacteria isolated in intensive care units in 2000 and 2002 at the AHEPA University Hospital, nearly half of all isolates of *P. aeruginosa* were found to be resistant to ciprofloxacin, imipenem and ticarcillin/clavulanic acid. Comparably, resistance rates for amikacin and piperacillin were relatively low. Lari *et al.* (1998:637), studying *Pseudomonas* infections at the Tohid Burn centre, Iran, also reported frequencies of *Pseudomonas* resistance to gentamicin, carbenicillin, co-trimoxazole, ceftizoxime and tetracycline to be over 95% and to amikacin to be 49%.

Abdi-Ali *et al.* (2005:196) investigated the bactericidal activity of various antibiotics on pseudomonal biofilms which they reported to play a role in up to 60% of human infections. They specifically investigated the effects of ceftazidime, imipenem, amikacin, gentamicin, ciprofloxacin, ofloxacin, azithromycin and erythromycin on *P. aeruginosa* in the biofilm and planktonic phase of growth in vitro. By their results, the β-lactam antibiotics imipenem and ceftazidime and the aminoglycosides, gentamicin and

amikacin, were found to be hardly effective on biofilm cells. Further to their report, the fluoroquinolones were seen to show strong bactericidal activity on the biofilm-forming cells as compared to other antibiotics. Biofilm cells grow slowly. This, coupled with reduction in the penetration of antibacterial agents through the biofilm layer according to the researchers, accounts for the decreased bactericidal activity of the β-lactam antibiotics which require rapid bacterial growth to kill cells.

Acquired resistance, mainly associated with growing antibiotic use among other factors is observed to be increasing particularly in ICU isolates (Ohl & Pollack, 2005:893). Quoting from an Intensive Care Antimicrobial Resistance Epidemiology (ICARE) project report on resistance of *P. aeruginosa* between 1998 and 2002, the authors reported increases of 14.5%, 10.5%, 13.7%, and 28.9% in resistance of the pathogen to piperacillin, ceftazidime, imipenem and ciprofloxacin respectively. The Lari *et al.* (1998:637) study referenced above also reported that resistance of *P. aeruginosa* to amikacin which was 49% in 1995 increased to 90% in 1997 and that with the introduction of ciprofloxacin at the burn centre in 1995 resistance of the pathogens to this antibiotic increased from 45% to 82% in 1997. Similarly in the Makedou *et al.* (2005:196) study as also referenced above, an upward trend in resistance of *P. aeruginosa* to all the antimicrobial agents studied in 2002 had been reported. This is in exception of ceftazidime for which resistance remained at 35%. These researchers also observed a dramatic increase in resistance of the pathogen to amikacin and tobramycin from 15% and 30% in 2000 respectively to a staggering 60% in 2002 for the two antibiotics. They also noticed that in 2002 resistance of the organism to piperacillin/clavulanic acid was 70% and that almost all antimicrobial agents studied were inactive against the microbe.

With the objective of finding antibiotics that could be used for treating infections of multidrug-resistant strains of *P. aeruginosa,* in vitro activities of non-traditional antimicrobials against the pathogens had also been investigated .Timurkaynak *et al.* (2006:227) in a study of this nature investigated the in vitro effects of colistin, rifampicin, meropenem, doxycycline and azithromycin and their combinations on multidrug-resistant strains of *P. aeruginosa*. Colistin, a polymycin antibiotic, primarily acts on the cell wall of gram-negative bacteria to cause rapid changes in the cytoplasmic cell membrane and ultimate cell death. Based on this known mechanism of action of the agent, the researchers postulated a synergistic activity between colistin and other antimicrobial

agents. In theory, colistin was expected to cause rapid permeation of outer cell membrane of gram-negative bacteria to allow other antimicrobial agents enhanced penetration and hence enhanced activity against the pathogens. Their investigations revealed that colistin demonstrated sensitivity rates of 89% against isolates of *P. aeruginosa* and had the best in vitro activity against the pathogen as compared with rifampicin, doxycycline, azithromycin, and meropenem. When combinations of these antimicrobials were tested against multidrug-resistant *P. aeruginosa* the researchers, Timurkaynak *et al.* (2006:227), found that,

- colistin plus rifampicin combination were very effective against *P. aeruginosa.* They showed synergistic action against two of five multidrug-resistant strains of the pathogen tested
- colistin plus meropenem and colistin plus azithromycin showed no synergistic activity against *P. aeruginosa*
- colistin and doxycycline demonstrated only partial synergism against four of five strains of multi drug resistant *P. aeruginosa*
- rifampicin and ampicillin/sulbactam act synergistically against multi drug-resistant *P. aeruginosa*

Reported as results of their literature search, Timurkaynak *et al.* (2006:227) also noted that azithromycin and ceftazidime or azithromycin and the quinolones are effective against multidrug-resistant strains of *P. aeruginosa*. Accordingly they concluded that azithromycin and rifampicin may be effective as components of combination treatment against multidrug-resistant strains of *P. aeruginosa.*

The above review has in summary established that the degree of sensitivity of pseudomonal isolates to the antipseudomonal antibiotics depends on the locality from which the isolates are obtained and the antibiotic usage pattern in that locality. It also showed that a sensitivity pattern in one locality can not be assumed to be the same as that in other localities. This is demonstrated for example in the Blandino *et al.* (2004:516), Makedou *et al.* (2005:246) and the Lari *et al.* (1998:637) studies where amikacin was shown as demonstrating the highest activity against *P. aeruginosa* in the first two studies and the least sensitivity in the last of the three studies. As in all cases of microbial antibiotic resistance development, the degree of resistance development of *Pseudomonas* to the antipseudomonal antibiotics seems to be associated with the extents of usage of individual antibiotics in a given locality. This is supported by results of the Lari *et al.* (1998:637) studies in particular which demonstrated alarming increases

in resistances of the most frequent antipseudomonal antibiotics used at their study sites. The review has also drawn attention to the special case of treating pseudomonal biofilm-forming cells which are reportedly involved in about 60% of human infections. These special pseudomonal cells have been shown by the Abdi-Ali *et al.* (2005:196) to be very resistant to many of the antipseudomonal antibiotics which otherwise displayed appreciable activities against planktonic cell types of the pathogen. It is of interest to note that the study cited the fluoroquinolones, ciprofloxacin and ofloxacin, among the antipseudomonal antibiotics tested as exhibiting the most activity against the pseudomonal biofilm forming cells considering the low levels of activities of these antibiotics against the pathogens as reported by other studies. The degree of effectiveness of the non-traditional antimicrobials, particularly of their combinations against multi-drug resistant strains of *P. aeruginosa* as reported by Timurkaynak *et al.* (2006:227) is also worth taking note of. In the face of the real problems associated with the treatment of pseudomonal infections and the fact that some of these traditional antibiotics are affordable by developing countries the findings of Timurkaynak *et al.* (2006:227), can be considered, pending clinical trials, as a welcome breakthrough development in the fight against *Pseudomonas*.

- **Antibiotic therapy in *Pseudomonas* infections**

Therapy in *Pseudomonas* infections involves the use of anti-pseudomonal antibiotics which, as indicated above generally includes the aminoglycosides, broad spectrum penicillins (e.g. piperacillin), third generation cephalosporins (e.g. ceftazidime) and the quinolones (e.g. ciprofloxacin) (Elliot *et al.* 2004:68). For treatment of various pseudomonas infections Ohl and Pollack (2005:895) suggested the treatment protocols listed in Table 2.7. For therapy of resistant *P. aeruginosa* infections the authors suggested antibiotic selections to be done on the basis of extended susceptibility testing. They also suggested increased treatment duration in such cases and where necessary, accompanied by surgical drainage or removal of infected tissues. Infections

Table 2.7 Recommended antimicrobial therapy for selected infections due to pseudomonas aeruginosa (Adapted from Ohl & Polack, 2005:895)

Anatomical site/Diagnosis	**Preferred therapy**	**Alternative therapy**	**Comments**
Bacteraemia, Endocarditis, Wound infections Pneumonia	**Anti-pseudomonal penicillins** [Piperacillin (3-4 g q 4 - 6 hrs IV) Piperacillin/tazobactam (3.375 g q 4 hrs IV) Mezlocillin (3 g q 4 hrs IV) Ticarcillin(3-4 g q4 -6hrs IV) Ticarcillin/clavulanate(3.1 g q4 - 6hrs IV)] **plus** **Aminoglycoside** Tobramycin MD: (2mg/kg load then 1.7mg/kg q 8 h IV) ODD: 5-7mg/kg q 24 hrs Gentamicin: MD & ODD: as for Tobramycin) Amikacin :MD 7.5 mg/kg load then7.5 mg/kg q 12 hrs IV ODD:15 mg/kg q 24 hrs IV	**Anti-pseudomonal penicillins plus Ciprofloxacin** (0.4g q12 hrs IV or o.5 - 0.75 g bid PO Levofloxacin 0.75g q 24 hrs IV or PO OR **Antipseudomonal cephalosporin** [Ceftazidime (2 g q 8 -12 h IV), Cefoperazone (2 g q 6 h IV) Cefepime (2 g q 8 hrs IV)] OR **Aztreonam (2 g q 6 - 8 hrs IV)** or **Carbapenem** [Imipenem/cilastin (0.5g q 6 hrs IV), Meropenem 1 g q 8 hrs IV)) **plus Aminoglycoside** or **Ciprofloxacin**	**Bacteraemia**: If due to infection associated with an indwelling catheter the catheter must be removed. Mono-therapy with antipseudomonal penicillin, cephalosporin, carbapenem or fluoroquinolone may suffice in absence of neutropenia, septic shock or life threatening co-morbidity. **Endocarditis**: Highest indicated doses of antibiotics required (Multi doses of aminoglycosides preferable to single daily doses). Serum aminoglycoside levels should be 10 x the minimum bactericidal concentration of antibiotic. **Wounds**: debridement required **Pneumonia**: Combination therapy should be employed initially if *P. aeruginosa* is suspected or conformed by culture **AIDS patients**: Repeated or prolonged therapy may be required.

Anatomical site/Diagnosis	Preferred therapy	Alternative therapy	Comments
			Cystic fibrosis: Inhalational therapy required 300 mg of tobramycin inhalation solution through jet nebulizer
Central nervous system	Ceftazidime alone or plus aminoglycoside	Cefepime or Ciprofloxacin (IV) or Aztreonam or meropenem	Drainage of brain abscess required. Intrathecal administration of antibiotic required if no response to IV administration.
Bone and joint	Anti-pseudomonal penicillins plus either Aminoglycoside or cephalosporin	Antipseudomonal cephalosporin Aztreonam or Carbapenem or Ciprofloxacin	4-6 week course of therapy required.
Malignant external otitis	Antipseudomonal or Carbapenem or Ciprofloxacin	Antipseudomonal penicillin cephalosporin plus aminoglycoside	Surgical debridement required usually. About 4 – 6 weeks of treatment is required.
Eye: Keratitis or corneal ulcers	Topical solutions of Tobramycin 14mg/ml alone or plus piperacillin or Ticarcillin 6- 12 mg/ml with	Topical solution of Ciprofloxacin or Ofloxacin (0.3%)	If combination therapy is used the second therapy should be administered 5 minutes after the first.
Endothalphmitis	Same as corneal ulcer plus intravitreal Amikacin (0.4 mg in 0.1 ml) or ceftazidime (2.25 mg in 0.1 ml	Same as corneal ulcer plus intravitreal Amikacin (0.4 mg in 0.1ml) or ceftazidime (2.25 mg in 0.1 ml	
Urinary tract	Ciprofloxacin	Aminoglycoside, or anti-pseudomonal penicillin or cephalosporin or carbapenem	
Dermatitis or folliculitis	None	None	

Abbreviations: MD, multidose; ODD, once daily dosing; PO, per oral or by mouth; IV, intravenous.

due to strains resistant to all commonly available antimicrobial agents may respond to parenteral or inhaled therapy with the relatively toxic antibiotics polymycin B and colistin (Ohl & Pollack, 2005:893).\

2.2 Mechanisms of bacterial resistance development to antibiotics

Bacteria achieve active drug resistance through three major mechanisms. These, according to Chambers (2001:1144) and Tenover (2006:S4), include the following:

- Efflux of the antibiotic from the bacterial cell through a collection of membrane associated pumping proteins.
- Modification of the antibiotic target through mutations of key binding elements such as ribosomal RNA or reprogramming of biosynthetic pathways.
- Synthesis of enzymes that selectively target and destroy the activity of antibiotics.

All these mechanisms require genetic programming by the bacterial cell in response to the presence of antimicrobial agents (Wright, 2005:1452). Genes required for such programming may be inherent in the bacterial cell or be acquired from other bacteria through transformation (*method of gene transfer information involving uptake of DNA from surrounding environment and its integration into host DNA)*), conjugation (*transfer of plasmid-encoded resistant genes by direct contact between two cells through a sex pilus or bridge*) or transduction (*acquisition of DNA from a bacteriophage that has incorporated such DNA from a previous bacteria*) (Tenover, 2006:S4; Chambers, 2001:1145,1146). By means of genetic exchange mechanisms many bacteria develop resistance to multiple classes of antibacterial agents (Tenover, 2006:S4). Susceptible populations of the bacteria following gene acquisition, develop resistance to antimicrobial agents through mutation. As Tenover (2006: S5) further stated, mutants ultimately become selected by antimicrobial use as a result of the antimicrobial agent killing the susceptible strains and allowing the newly resistant strains to survive and grow.

2.2.1 Efflux pump systems in bacterial pathogens

Efflux pump systems for antibiotics as a mechanism of pathogen resistance development operate in both gram-positive and gram-negative organisms (Zhong & Shortridge, 2000:325&326). They involve antiport mechanisms which in most cases are coupled to a protonmotive force (pmf) that entail exchange of a proton for a drug cation

complex (Chopra, 2002:120) or the use of ATP as energy source (Chopra, 2002:121; Lynch, 2006:949). They are coded by genes which can either be acquired or carried intrinsically according to further indications by Zhong and Shortridge (2000:325&326). Examples include the following:

- Efflux pump systems for macrolide resistance development in *Streptococcus pneumoniae* and *Streptococcus. pyogenes,* where they are encoded respectively by *mefE* and *mefA* genes or *mef(A)* genes as they are now referred for both organisms because of their close structural similarities. The pump systems encoded by *mef* are effective resistance development mechanisms against 14 and 15-membered ring macrolides (erythromycin, clarithromycin and azithromycin) in streptococci but much less so against the ketolides, e.g. telithromycin (Shortridge,1999:132). In contrast to streptococci, the system is a much less clinically significant mechanism of resistance in staphylococci (Zhong & Shortridge, 2000:325 and 326).
- Export of tetracycline from cells mostly by pmf dependent efflux mechanisms encoded by tetracycline resistant or *tet* genes. The genes encode membrane associated proteins which export the drugs from the cells. The efflux pump systems also appear to use ATP rather than the pmf as energy source as seen in *Corynebacterium striatum*. The *tet* encoded efflux systems operate both in gram-negative and gram-positive bacteria. (Chopra, 2002:120).
- Efflux mechanisms of enterococci in chloramphenicol, tetracycline, and quinolone resistance development (Klare *et al.*, 2003:277)
- Energy dependent intrinsic multidrug efflux systems for which quinolones and other antibiotics are substrates operate in a number of bacteria including *E. coli, P. aeruginosa* and *S. aureus* (Li, 2005:454). In *S. aureus,* for example, the efflux pump NorA is responsible for decreased susceptibility to fluoroquinolones. Hydrophilic quinolones such as norfloxacin, ciprofloxacin and ofloxacin particularly are effectively pumped out of bacterial cells by this system and has resulted in the limited use of the these antibiotics in some clinical settings (Dougherty *et al.*, 2001:532).

A number of multidrug efflux pumps have been identified in gram-negative bacteria. This group of bacteria export antibiotics from their intracellular to extracellular spaces through two membrane arrangements due to their structurally characteristic inner membrane (IM) and outer membrane (OM) arrangement with intervening periplasmic space. For reasons of the export of drugs having to be done through these two membrane arrangements, a drug transport or efflux system in which IM pump proteins are transiently or permanently

associated with outer membrane channel proteins are required. In this arrangement, efflux complexes traverse both the inner and outer membranes and facilitate direct passage of the substrate from the cytoplasm or the cytoplasmic membrane into the external medium (Zgurskaya & Nikaido, 2000: 219). Gram-negative bacteria thus, are seen to possess efflux pump systems that are composed of tri-partite transport systems involving specific interactions between an IM pump protein, an OM channel protein and a membrane fusion protein (MFP). All three components of the efflux system are often coded in the same gene cluster as exemplified in the AcrA-AcrB-TolC (or AcrAB-TolC) systems of *Escherichia coli* and *H. influenzae*, the MexA-MexB-OprM (or MexAB-OprM) system of *Pseudomonas aeruginosa* and MtrCDE of *N. gonorrhoea* (Lynch, 2006:950). These efflux systems are known to be responsible for the organisms' resistances to the macrolides (Zhong & Shortridge, 2000:326).

2.2.2 Modification of antibiotic targets and reprogramming of biosynthetic pathways

Modification of the antibiotic target may be due to any one of the following mechanisms and include, as stated by Chambers (2001:1145), mutation or modification of the natural target of the antibiotic or the substitution of native susceptible target with an alternative target to which the antibiotic does not bind.

Modification of ribosomal RNA (rRNA), for example, is a means by which a number of pathogens may develop resistance to antibiotics. The ribosome is a large enzyme that is involved in protein synthesis. It decodes information stored in messenger RNA (mRNA) during protein synthesis and catalyses sequential incorporation of amino acids into growing peptide chains (Doi & Arakawa, 2007:89; Vakulenco & Mobashery, 2003:432). It is a complex structure comprising three RNA molecules and more than 50 proteins. In bacteria, it consists of two subunits referred to as 50S and 30S according to their sedimentation rates. The larger of the two subunits has two RNA molecules known as 5S and 23S RNA while the smaller has one RNA molecule named 16S RNA. (Vakulenco & Mobashery, 2003:431). As their mechanisms of actions, some antibiotics (macrolides, lincosamides, streptogramins, tetracyclines, chloramphenicol and aminoglycosides) bind these ribosomal RNAs to disrupt protein synthesis in the bacteria (Table 2.8). Resistance may result from modifications of rRNAs due to reduced affinity of the antibiotic to bind to the critical target. In other instances it may be due to failure of the

antibiotic to bind to the target due to substitution for the native target with a new target to which the antibiotic does not bind (Chambers, 2001:1145; Chopra, 2005:121). Other types of antibiotic target modifications may occur as mechanisms of antibiotic resistance development as exemplified below:

- Development of acquired resistance by some pathogens to quinolones. Acquisition of resistance of the quinolones is mediated mainly by chromosomal mutations that either alter targets of the quinolone drugs or activate expression of multidrug-resistant efflux systems as already indicated (Li, 2005:454). Drug targ*et al*terations according to the author most frequently occur to the *gyr*A gene, within a small limited region of the gene called the "quinolone resistance determining region" (QRDR). The resistances are demonstrated by many organisms including *E. coli, P. aeruginosa, S. aureus, enterococci, Campylobacter jejuni, Salmonella spp* and *N. gonorrhoea* (Li, 2005:454; Klare *et al.*, 2003:277; Escribano *et al.*, 2004:428-432).
- Production of ribosomal proteins which, in tetracycline resistance for example, appear to promote GTP- dependent release of tetracyclines from the ribosomal A site leading to dissociation of the antibiotic from the target (Chopra, 2002:119-123).
- The demonstration of resistance by clinical isolates of *S. pneumoniae* against β-lactam antibiotics. This is recognised to be due to the organisms' acquisition of mutations of their transpeptidases (TP) domains of penicillin binding proteins (PBPs) by means of homologous events with related species (Contreras-Martel *et al.*, 2006: 685).

2.2.3 Enzymatic destruction of the activity of antibiotics

Drug inactivation is an important mechanism of pathogens' resistance to antibiotics. In many cases, the antibiotic may become enzymatically destroyed by enzymes produced by bacteria as in the production of β-lactamases and aminoglycoside modifying enzymes in the respective cases of microbial resistance to β-lactam and aminoglycoside antibiotics. In the cases of prodrugs that may need to be converted to the active metabolites of the antimicrobial agents before demonstration of activity, the bacterial cell may show resistance by failing to convert the prodrug into the active metabolite. This is seen in the case of resistance development of *Mycobacterium tuberculosis* to isoniazid (Chambers, 2001: 1144). Major examples of these mechanisms of bacterial pathogens resistance development are as outlined below:

- Bacteria evasion of killing by β-lactam antibiotics through the development of β-lactamase (penicillinase) enzymes that acylate and hydrolytically breaks up β-lactam rings and transform the lactams into the corresponding innocuous acids (Marrero *et al., 2006:507;* Babic *et al.*, 2006:147).
- Development of extended spectrum β-lactamases (ESBLs) by Enterobacteriaceae e.g. *E. coli* and *Klebsiella* spp. ESBLs have extended hydrolytic activities against antibiotics like ceftazidime and cefotaxime that are known to resist hydroxylation activities of the usual β-lactamases found in *E. coli* and *Klebsiella* spp (Babic *et al.*, 2006:147). Generally ESBLs are capable of hydrolysing the penicillin (ampicillin & piperacillin) cephalosporins of the first, second, third and fourth generations and the monobactams, aztreonam, but not the cephamycins (cefoxitin and cefotetan) and carbapenems. They demonstrate enhanced susceptibility to inhibition by β-lactamase inhibitors (i.e. clavulanic acid, tazobactam or sulbactam) though β-lactam/β-lactamase inhibitor combinations are not seen to be universally effective against *E. coli* and *Klebsiella* spp containing ESBLs (Perez *et al.*, 2007:459; Babic *et al.*, 2006:147). The production of other β-lactamases, considering the complex genetic background of bacterium, seems to attenuate the efficacy of β-lactamase inhibitors. The plasmid mediated AmpC-type of β-lactamases for example hydrolyses the 2nd generation cephalosporins, cefoxitin and cefotetan (α-methoxy cephalosporins or the cephamycins. (Babic *et al.*, 2006:147,149; Melano *et al.*, 2006:197). Also β-lactamase production in combination with loss or down-regulation of porins, a transport route of antibiotics into cells of gram-negative bacteria are seen to partly account for the resistance of some strains of ESBL producing bacteria against β-lactam/β-lactamase inhibitor combinations. It is reported that ESBL-producing strains can become resistant to cefoxitin due to decreased or loss of outer membrane proteins creating porins in surface membranes of gram-negative bacteria (Melano *et al.*, 2006:203).

Apart from β-lactamases, other enzymatic mechanisms of resistance by antibiotic inactivation are also encountered in some bacterial pathogens. Some of these as noted by Wright (2005:1454 -1464), include the following:

- The formation of **macrolide esterases** in some bacteria. This is notably seen in *E. coli* and *Providentia stuartii* and also certain clinical isolates of *S. aureus* and *Pseudomonas spp.* They confer high levels of macrolide resistance in organisms liberating them. The enzymes hydrolyse ester bonds that are formed in cyclization

processes of macrolides during the antibiotics' mechanisms of interference of protein synthesis in the organism.

- The formation of enzymes that transfer chemical functional groups to antibiotics to modify their structures covalently and impair their binding to target sites in the bacterial cell. Important examples include:
  - **acyltransferases** which transfer acyl functional groups to vulnerable hydroxyl and/or amine groups in the antibiotic;
  - **aminoglycoside acetyltransferases** which transfer acetyl groups to key hydroxyl and amine groups on aminoglycoside antibiotics. This disrupts the interaction of the antibiotics with their binding sites on bacterial ribosomes to result in resistance development. .
  - **chloramphenicol acetyltransferases** liberated by *E. coli* and *Pseudomonas* spp and which are involved in O-acetylation and structural modification of chloramphenicol;
  - **streptogramin acetyltransferases** which inactivate type A streptogramins by acetylation of the free hydroxyl group at position 14 of the molecule. Genes encoding these enzymes have been identified in a number of gram-positive bacteria including the staphylococci and enterococci.
  - **Aminoglycoside kinases** which are primarily found in gram-positive cocci such as staphylococci and enterococci. They confer resistance to a broad range of aminoglycosides but not gentamicin and tobramycin which both lack a critical 3'-hydroxyl group that accepts the phosphate group donated by ATP. The enzymes are involved in the phosphorylation of the antibiotics to effect changes which dramatically reduces the ability of the antibiotic to bind to their targets.

2.3 Exploiting mechanisms of pathogen antibiotic resistance in the development of new antibiotics.

2.3.1 Antibiotic discoveries based on efflux technologies

Knowledge of the characteristics of specific efflux systems have been employed largely in efforts to discover new antibiotics that circumvent such systems. Examples of antibiotics discovered from such knowledge base include typically glycylcycline (tigecycline) and the ketolide, telithromycin (Lynch, 2006:951). The two antibiotics which are respective congeners of tetracycline and the macrolides differ from the parent

compounds by their lack of affinities for efflux pumps that extrudes the indicated antibiotics from the bacterial cells to circumvent their activities.

- **Tigecycline (glycylcycline)**

  The antibiotic is different structurally from the tetracycline by having a tert-butyl-glycylamido side chain added to carbon 9 of the D ring of the tetracycline nucleus of the parent compound, minocycline (Doan *et al.*, 2006:1081). It circumvents specifically a series of MFS (major facilitator family) class of tetracycline-specific efflux proteins of both gram-negative and gram-positive pathogens and exhibits as a result superior activity against clinical isolates of pathogens bearing such activated efflux systems (Lynch, 2006:951).

- **Telithromycin**

  Telithromycin is a ketolide in which the L-cladinose moiety at C-3 of the macrolide ring was substituted with a keto group. This was coupled with an introduction of a group at C-6 of the ring and a large N-substituted carbamate extension at C-11/C-12 (File, 2005:S363; Nilius & Ma, 2002:4). The modifications of the macrolide resulted in inhibition of macrolide efflux manifesting through MefA/E and AcrAB systems and an elevation of the activity of the antibiotic to about 10 times that of erythromycin against clinical isolates operating resistance mechanisms with the pump system File 2005: S364).

- **Fluoroquinolones**

  Older generation fluoroquinolones, namely, ciprofloxacin, norfloxacin and ofloxacin, are hydrophilic and are effectively pumped out by NorA or similar efflux pump systems of gram-positive cocci, limiting the use of these antibiotics in treating infections by these pathogens. Structural modifications of these antibiotics to produce more hydrophobic agents results in the discovery of the newer fluoroquinolones (8-methoxy quinolones) such as, trovafloxacin, gatifloxacin and moxifloxacin which are not affected by these pump systems (Dougherty *et al.*, 2001:532). While their improved activity against gram-positive may be attributed to this, Appelbaum and Hunter (2000:10) are of the opinion that the improved activity of the newer fluoroquinolones is probably a combination of an enhanced activity against the targets DNA gyrase and topoisomerase IV and an observed lower rate of selection of resistant mutants.

- **Efflux pump inhibitors on clinical trials**

  One drug development program which involved the co-administration of an efflux pump inhibitor to potentiate the actions of antibacterial agents reached the second phase of human clinical trials conducted by Mpex Pharmaceuticals by 2006 (Lynch, 2006:952). Administered as an aerosol, the agent (MP-601205) was given concurrently with ciprofloxacin for the treatment of pulmonary exacerbations in cystic fibrosis. Compared with other pump inhibitors, published data indicated that the compound inhibited the endogenous activity of fluoroquinolone pump systems to extents that can result in hypersensitisation of *P. aeruginosa* to ciprofloxacin to a level consistent with improved efficacy (Lynch, 2006:952). A search of the literature did not reveal results of the human clinical trials of the use of MP601205 to potentiate the effects of ciprofloxacin in treating *P. aeruginosa* infections in exacerbated cystic fibrosis as indicated. Bostian *et al.* (2008:1), however, patented MP-601205 for the treatment of ophthalmic and otic infections (Patent: US2008/0132457A1) to indicate a successful application of this compound as a current advance in the use of efflux inhibitors to augment the effects of antibiotics in treating certain infections.

2.3.2 β-lactam antibiotic/β-lactamase-inhibitor combinations

Inactivation of β-lactamases to enable the use of β-lactam antibiotics in treating infections caused by β-lactamase producing organisms had been investigated and led to the successful introduction and use of β-lactam antibiotic/β-lactamase-inhibitor combinations in treating infections caused by β-lactamase producers. Inhibitors currently employed for this purpose include clavulanic acid, sulbactam and tazobactam (Buynak, 2006:931).The inhibitors are most active against plasmid-encoded β-lactamases or Ambler class A enzymes which remain the most commonly encountered. It includes extended-spectrum ceftazidime and cefotaxime-hydrolysing enzymes (Chambers, 2001:1214; Buynak, 2006:931). Current β-lactam antibiotic/β-lactamase-inhibitor combinations available for use according to Buynak (2006:931) include the following:

- Amoxicillin clavulanic acid (Trade name: Augmentin)
- Ticarcillin/clavulanic acid (Trade name: Timentin)
- Ampicillin/sulbactam (Trade name: Unasyn) and
- Piperacillin/tazobactam Trade name: (Zosyn)

2.4 Antibiotics: Classification and characteristics, mechanisms of actions and clinical applications

Antibiotics generally are defined in the strictest sense as substances that are produced by various species of microorganisms that suppress the growth of other microorganisms (Chambers, 2001:1143). In common usage, however, the term according to the author is often extended to include synthetic antimicrobial agents such as the sulphonamides and the quinolones. They are referred to as semisynthetic when they are chemically altered to improve their properties, e.g. stability or spectrum of activity (Elliot *et al.*, 2004:177).

Classification of antibiotics is based most commonly on the chemical structures and mechanisms of action of the agents. Employing these principles, Chambers (2001:1143) and Elliot *et al.*, 2004 177-188), classified antibiotics fundamentally into the following groupings

- Agents that inhibit synthesis of bacterial cell wall
- Agents that act directly on the cell membrane of the microorganisms
- Agents that affect the function of 30S or 50S ribosomal subunits to cause a reversible inhibition of protein synthesis
- Agents that bind to 30S ribosomal subunit and alter protein synthesis leading to ultimate cell death
- Agents that affect bacterial nucleic acid synthesis

Individual agents belonging to the above classifications are reviewed in Tables 2.8 and 2.9. in respect to their structural descriptions and properties, mechanisms of action and modes of bacterial development of resistance against them (Table 2.8). Their spectra of activity as well as their therapeutic applications, adverse effects and drug interactions were also reviewed and presented in Table 2.9.

Table 2.8 Classifications and mechanisms of action of antibiotics (Compiled from Elliot *et al.*, 2004 177-188; Chambers 1143 -1266 and other literature as indicated)

ANTIBIOTICS: SUBCLASSES & EXAMPLES	STRUCTURAL DESCRIPTION AND PROPERTIES	MECHANISM OF ACTION & MODE OF BACTERIAL RESISTANCE DEVELOPMENT
A. AGENTS THAT INHIBIT SYNTHESIS OF BACTERIAL CELL WALL		
β - lactam antibiotics Examples:	These have a β - lactam ring in their chemical structure.	• **Mechanism of action** – Bactericidal. – β - lactam ring is important to the activities of these antibiotics. They inhibit the last step in bacterial peptidoglycan synthesis in cell wall which involves formation of cross linkages of the petidoglycans (Marerro *et al.*, 2006:507). The transpeptidase enzyme involved at this stage of the cell wall synthesis is acetylated by the β - lactam antibiotics with a cleavage of the -CO-NO- bond of the β - lactam ring (Marerro *et al.*, 2006:507; Chambers, 2001:1143-1190). This leads to cell lysis and death of the bacteria. – β - lactam antibiotics also bind to target proteins referred to as penicillin binding proteins (PBPs). All bacteria are known to have PBPs They vary in their affinities for different β - lactam antibiotics and have varied functions in the bacteria. For some bacteria e.g. *E. coli* these are transpeptidases involved in peptidoglycan synthesis or maintenance of the pathogens rod like shape. Their binding
Penicillins		
– Penicillin G – Penicillin V	Readily hydrolysed by penicillinase; Ineffective against most strains of *S. aureus*.	
Penicillinase resistant penicillins		
– Isoxazolyl penicillins: Oxacillin, Cloxacillin dicloxacillin – Nafcillin	Resistant to staphylococcal penicillinase. Much less active than **penicillin G** is against other penicillin active microorganisms and are not to be used as substitutes for treating infections amenable to penicillin G Rapidly but incompletely absorbed. Absorption more efficient if taken on empty stomach. **Nafcillin** is the most active of the penicillinase - resistant penicillins against other microorganisms but is not as potent as penicillin G. its absorption from the gastrointestinal tract is erratic and is preferably given by parenteral routes.	

ANTIBIOTICS: SUBCLASSES & EXAMPLES	STRUCTURAL DESCRIPTION AND PROPERTIES	MECHANISM OF ACTION & MODE OF BACTERIAL RESISTANCE DEVELOPMENT
Aminopenicillins: Ampicillin, amoxicillin, and their congeners	The **Aminopenicillins** are stable in acid and are well absorbed. Food intake results in less complete absorption. Severe renal impairment requires dose adjustment. It appears in bile and undergoes hepatic circulation with loss of the antibiotic in the faeces. **Ampicillin** and **amoxycillin** have identical pharmacological properties and the same spectrum of activity. Amoxicillin unlike ampicillin is more rapidly and completely absorbed from the gastrointestinal tract. It is less effective than ampicillin however in shigellosis. **Amoxycillin** is the most active of all oral β - lactam antibiotics against penicillin sensitive and penicillin resistant organisms.	with the β - lactam antibiotics disrupts the shape of the bacteria to cause spheroblast formation and death of the cell.
Antipseudomonal penicillins Include the Carboxypenicillins – Carbenicillin – Ticarcillin and the Ureidopenicillins – Mezlocillin – Piperacillin	These demonstrate activity against *P. aeruginosa* and some strains of *Proteus* resistant to ampicillin. The **ureidopenicillins** have superior activity against the **Carboxypenicillins**. Both types of antibiotics can be destroyed by β - lactamases. **Ticarcillin** is more active than **carbenicillin** but less so than mezlocillin and piperacillin against *Pseudomonas*. **Mezlocillin** is more active against *Klebsiella* than is carbenicillin and is more active than ticarcillin against *Enterococcus faecalis*. **Piperacillin** is active against most strains of *P. aeruginosa* and non β - lactamase producing *Enterobacteriaceae*	• **Mode of bacterial resistance development** – Main mode of bacteria pathogens' resistance development is through the production of β-lactamase enzyme production (Marrero *et al.2006:507;* Babic *et al.*, 2006:147).
Cephalosporins	These have a β - lactam ring bound to a six member dihydrothiazine ring. Modification at position 7 of the β - lactam ring alters antimicrobial activity. Substitution at position 3 of the dihydrothiazine	• **Mechanism of action** Bactericidal

ANTIBIOTICS: SUBCLASSES & EXAMPLES	STRUCTURAL DESCRIPTION AND PROPERTIES	MECHANISM OF ACTION & MODE OF BACTERIAL RESISTANCE DEVELOPMENT
	ring alters the metabolism (toxicity) and pharmacokinetic properties of the antibiotics Cephalosporins are mainly eliminated by the renal route. Dosage adjustment required in kidney failure (Chambers, 2001:1210).	Mechanism of action similar to that of the penicillins. Cephalosporins bind to PBPs and so inhibit various bacterial functions leading to cell lysis. Penetration of the antibiotic through the outer cell wall and remaining resistant to hydrolysis by β - lactamases are very crucial to the activity of the antibiotics. • **Mode of bacterial resistance development** Chambers (2001:1209), indicated the following as major modes of resistant development of bacterial pathogens to the cephalosporins: – Hydrolysis of β - lactam ring by β - lactamases. The agents have variable affinity for β-lactams. Cefoxitin, cefuroxime and the TGCs e.g. are more resistant to hydrolysis by β - lactamases produced by gram -ve bacteria than 1st generation agents. TGCs are susceptible to hydrolysis by inducible chromosomally encoded (type I) β - lactamases. FGCs are poor inducers of type I β - lactamases and are less susceptible to hydrolysis by type Iβ - lactamases than are the TGCs.
1st Generation – Ceftazolin – Cephalothin – Cephalexin – Cephradine – Cefadroxil	Cefazolin and cephalothin are similar in their spectra of activity, though the former is more active against susceptible organisms (*E. coli, Klebsiella and β - lactamase producing S. aureus*). Cephalothin is not well absorbed and is available for parenteral administration only. Cephalexin, cephradine and cefadroxil are similar in activity to cefazolin and cephalothin. Cephalexin is available for oral administration but is les active against β - lactamase producing *S. aureus*. It is not metabolised and is 100% renally eliminated. Cephradine and cefadroxil are similar in structure to cephalexin and can all be orally administered.	
2nd Generation (SGC) – Cefamandole – Cefoxitin (cephamycin) – Cefotetan (cephamycin) – Cefuroxime – Cefaclor – Cefotetan – Cefditoren	2nd generation cephalosporins are more active against gram-negative bacteria than the 1st generation group of the antibiotics. They have broader spectrum and are active against Enterobacter spp, indole-positive *Proteus* and *Klebsiella*. **Cefoxitin** (cephamycin) is more active than other 1st and 2nd generation agents (except cefotetan) against anaerobes particularly *B. fragilis*. It has its main use in treating anaerobic and mixed anaerobic infections. **Cefotetan** (also a cephamycin) has good activity against *B. fragilis* and other spp of *Bacteroides*. **Cefaclo**r is more active against *H influenzae* and *Moraxella catarrhalis* and is used orally. **Cefuroxime** is similar	

ANTIBIOTICS: SUBCLASSES & EXAMPLES	STRUCTURAL DESCRIPTION AND PROPERTIES	MECHANISM OF ACTION & MODE OF BACTERIAL RESISTANCE DEVELOPMENT
– Cefdinir	to **Cefamandole** but is more resistant to β - lactamase degradation. It is effective but less than ceftriaxone in treating meningitis due to *H. influenzae* (including strains resistant to ampicillin) and *N. Meningitidis* and *S pneumoniae*. **Cefuroxime axetil** is available as the oral form of cefuroxime. **Cefditoren**, **cefdinir** and **cefpodoxime** (oral 3rd generation) all have good activity against most respiratory pathogens and methicillin susceptible *S. aureus* (Archer & Polk, 2005:798)	
3rd Generation (TGC) – Cefotaxime – Ceftriaxone – Ceftazidime – Cefoperazone – Cefpodoxime (oral) – Cefixime (oral)	3rd generation cephalosporins all have a broad spectrum of activity against enteric gram-negative bacilli. Gram-positive spectra of the class are variable but all are less than those of the 1st generation (Archer & Polk, 2005:798). **Cefotaxime** is highly resistant to many bacterial β - lactamases but not the extended β - lactamases (ESBLs). It has good activity against many gram-positive and gram-negative aerobic bacilli. **Deacetylcefotaxime**, a metabolite of the cefotaxime, acts synergistically against certain microbes. **Ceftriaxone** has activity very similar to that of cefotaxime but has a long half life of 8 hrs as a distinguishing feature. The drug can be administered once or twice (for meningitis) and once to treat other infections. **Cefixime** and **cefpodoxime proxetil** are oral forms of the 3rd generation cephalosporins. They are similar in activity but cefpodoxime has a higher activity against *S. aureus*. They are less active compared to the oral 2nd generation agents against gram-	

ANTIBIOTICS: SUBCLASSES & EXAMPLES	STRUCTURAL DESCRIPTION AND PROPERTIES	MECHANISM OF ACTION & MODE OF BACTERIAL RESISTANCE DEVELOPMENT
	positive cocci and more active against Enterobacteriaceae and β - lactamase producing *H. influenzae, M. catarrhalis* and *N. gonorrhoea.* **Cefoperazone** and **ceftazidime** are considered pseudomonas cephalosporins. Cefoperazone is less effective than cefotaxime against gram-positive microorganisms and many gram-negative bacteria but more active than it against *P. aeruginosa.* Ceftazidime has an excellent activity against *P. aeruginosa* as its major distinguishing feature. It is more active against *P. aeruginosa* than cefoperazone, and piperacillin.	
4th Generation (FGC) – Cefepime – Cefpirome	Cefepime is stable to hydrolysis by many plasmid encoded β - lactamases. It is a poor inducer of type 1 chromosomally encoded and some other types of ESBLs. It is active against Enterobacteriaceae resistant to other cephalosporins that induce type 1 chromosomally encoded and some other ESBLs. It is active against many bacteria expressing extended spectrum plasmid mediated ESBLs. Cefepime has comparable activity with Ceftazidime against *P. aeruginosa.* It is 100% renally eliminated.	
Penems [(Clinical Laboratory Standards Institute (CLSI)] new name for carbapenems.	The penems, by CLSI renaming of carbapenems according to Dalhoff *et al.* (2001:1086) are β - lactam antibiotics that contain a fused β - lactam ring and a 5-membered ring system that differs from penicillins in being unsaturated. It has two subclasses namely the "penems" which have a "sulphur" at position 1 of the 5-membered ring and the "carbapenems" which have a "carbon"	• **Mechanism of action** Bactericidal Binds to high molecular weight PBPs and inhibit bacteria transpeptidases involved in peptidoglycan synthesis of bacterial cell wall

ANTIBIOTICS: SUBCLASSES & EXAMPLES	STRUCTURAL DESCRIPTION AND PROPERTIES	MECHANISM OF ACTION & MODE OF BACTERIAL RESISTANCE DEVELOPMENT
	instead of a "sulphur" at position "1" of the ring. The penems share in common a double bond between positions C.2 and C3 conjugated to the β - lactam nitrogen which, like the cephalosporins, increases the reactivity of the β - lactam ring to various nucleophiles. The C-6 side chains of the penems are oriented on the opposite side of the β - lactam ring compared to analogous positions of penicillins and cephalosporins. This stereochemical configuration conferred on the penems a remarkable stability to degradation by β - lactamases	formation and repair. (Darville, 1999:38). • **Mode of bacterial resistance development** The followings are of note with respect to bacterial resistance development to the carbapenems according to Knapp and English (2001:175 &176), – Carbapenems are stable against most β - lactamases but not metallo β - lactamases. Organisms e.g. *Bacteroides*, *Stenotrophomonas maltophilia* and some *Bacillus* that express the metallo β - lactamases are intrinsically resistant to the agents. – *Enterococcus faecum* is intrinsically resistant to the carbapenems because they possess PBPs that the agents do not inhibit.
Carbapenems **Examples**	They show significant post antibiotic effect against gram-negative bacteria similar to aminoglycosides and fluoroquinolones in contrast to other β - lactam antibiotics (Knapp & English, 2001: 175)	
– Imipenem – Meropenem – Ertapenem – Doripenem	**Imipenem** is co-admitted with cilastatin to prevent hydrolysis by renal dihydropeptidase-1 (DHP-1) and also nephrotoxicity seen with imipenem alone. **Meropenem** has a β - methyl side chain which makes it stable to DHP-1. Both drugs are unstable at 25-37 °C degraded by 70% and 60% respectively at 37 °C within 24 hrs (Dalhoff *et al.*, 2006:1087). Imipenem is not absorbed orally. It acts as a strong and meropenem a weak inducer of ESBL production (Dalhoff *et al.*, 2006:1090) **Doripenem** is an investigational carbapenem. Its advantages over the other carbapenems include enhanced stability and activity against *P. aeruginosa*, with a low propensity for resistance. Has the lowest potential for seizures in the carbapenem class and the greatest stability after reconstitution (*Jones et al.*, 2004:3139; Mushtaq *et al.*, 2004:3091)	

ANTIBIOTICS: SUBCLASSES & EXAMPLES	STRUCTURAL DESCRIPTION AND PROPERTIES	MECHANISM OF ACTION & MODE OF BACTERIAL RESISTANCE DEVELOPMENT
Penems		
Faropenem	Differs from the carbapenems by lacking a protonable C-2 side chain. This makes the drug to show remarkable chemical stability, discomposing by only 6%, in a neutral pH aqueous solution at 37 °C. In the form of faropenem the medoxomil the agent is rapidly absorbed upon oral administration. It is the only penem available for oral use and provides a means of sequential use (switching from parenteral to oral use) of the penems (Dalhoff *et al.*, 2006:1088 & 1089).	
Aztreonam	Monocyclic β-lactam (monobactams) antibiotic in which the β-lactam ring is not fused with the 5 or 6 membered rings of the penicillins, cephalosporins or penems. The antibiotic is administered intramuscularly or intravenously. Its half life of 1.7 hours is prolonged in anephric patients and requires dosage adjustment in renal insufficiency.	• **Mechanism of action** Interacts with PBPs of susceptible organisms to produce the formation of filamentous bacterial structures.
Glycopeptides – Vancomycin – Teicoplanin	These are unusual complexes of tricyclic glycopeptides with large molecular masses. Vancomycin has a molecular mass of about 1500 daltons (Chambers, 2001:1262,1264). Vancomycin and Teicoplanin are poorly absorbed and are administered, vancomycin intravenously and teicoplanin, intravenously and intramuscularly.	• **Mechanism of action** Bactericidal (for dividing cells) Due to its size and hydrophobicity the glycopeptides cannot penetrate the cytoplasmic membrane. They inhibit cell wall synthesis by

ANTIBIOTICS: SUBCLASSES & EXAMPLES	STRUCTURAL DESCRIPTION AND PROPERTIES	MECHANISM OF ACTION & MODE OF BACTERIAL RESISTANCE DEVELOPMENT
	The drugs are eliminated mainly renally. Dose adjustment is required in renal insufficiency (Chambers ,2001:1262)	binding with high affinity to the C-terminal D-alanyl-D-alanine of cell wall precursor units. The complex formed blocks the transglycosylation and transpeptidation reactions, the activity of carboxypeptidases and the incorporation of the precursors into bacterial cell wall (Chambers 2001:1262; Gholizadeh & Courvalin, 2000:S11; Klare *et al.*, 2003:271).
B: AGENTS THAT AFFECT THE FUNCTION OF 30S OR 50S RIBOSOMAL SUBUNITS TO CAUSE A REVERSIBLE INHIBITION OF PROTEIN SYNTHESIS		
Antibiotics within classification	**Structural description and notes on properties of individual antibiotics**	**Mechanism of action**
Chloramphenicol	Is a derivative of dichloroacetic acid and contains nitrobenzene moiety. Parenteral preparation of the drug is in the inactive prodrug sodium succinate. Esterases in the liver, kidneys and lungs may all be involved in the hydrolysis of the prodrug into the active form. The prodrug itself is rapidly cleared form the plasma by the kidneys. This may affect the bioavailability of the active drug as 20% to 30% of the dose may be excreted prior to hydrolysis to the active form. Poor renal function of neonates and conditions of renal insufficiency may result in increased plasma concentrations. Decreased esterase activity in neonates and infants results in prolonged periods in reaching peak concentrations of active chloramphenicol. This gives a longer period over which clearance of chloramphenicol succinate	• **Mechanism of action** Bacteriostatic. May be bactericidal to other bacteria e.g. *H. influenzae, N. meningitidis and S. pneumoniae* Inhibits protein synthesis in bacteria by reversibly binding and competitively inhibiting 50 S ribosomal subunits. Inhibition of the subunit prevents the binding of the amino acid containing end of the aminoacyl tRNA to the acceptor site on the 50 S ribosomal subunit. This inhibits the interaction between peptidyltransferase and its amino acid substrate and hence peptide bond

ANTIBIOTICS: SUBCLASSES & EXAMPLES	STRUCTURAL DESCRIPTION AND PROPERTIES	MECHANISM OF ACTION & MODE OF BACTERIAL RESISTANCE DEVELOPMENT
	can occur. Clindamycin and the macrolide antibiotics bind near the binding site of chloramphenicol on 50 S ribosomal subunits. These drugs may interfere with the each other's antimicrobial action if given concurrently (Chambers, 2001:1247:)	formation. (Chambers, 2001:1247; Elliot *et al.*, 2004 182)
Tetracyclines Examples: – Tetracycline – Chlortetracycline – Demeclocycline – Oxytetracycline – Tetracycline – Doxycycline – Minocycline	The tetracyclines are close congeners of polycyclic naphthacenecarboxamide. Minocycline, doxycycline and tetracycline in that order are more lipophilic and more active. Absorption of the tetracyclines occurs in the stomach and upper small intestine. It is often incomplete for most of the drugs. It is highest in the fasting state and is impaired with concurrent administration with diary products, divalent and trivalent metal ion drug preparations and bismuth subsalicylate. Food does not affect the absorption of doxycycline and minocycline. Percentage of oral dose that is absorbed is lowest for chlortetracycline (30%), intermediate for oxytetracycline, demeclocycline and tetracycline (60% - 80%) and high for doxycycline (95%) and minocycline (100%). Percentage of unabsorbed drug increases with increase in dose. Doxycycline and minocycline are given in lower daily dosages by the oral route than tetracycline oxytetracycline and demeclocycline because they have higher half lives (16 to 18 hours) and are better absorbed. The drugs distribute widely through out the body into tissue and	• **Mechanism of action** Bacteriostatic to bacterial cell growth. Tetracyclines inhibit bacterial protein synthesis by binding to the 30S bacterial ribosome subunit and blocks access of aminoacyl tRNA to the acceptor (A) site on the mRNA-ribosome. The process results in blockade of amino acid chain elongation. • **Mode of bacterial resistance development** Resistance of *E. coli* to tetracyclines is primarily plasmid mediated and is an inducible trait. Resistance mechanisms involved include, – decreased intracellular accumulation of tetracycline as a result of decreased influx or acquisition of energy dependent efflux pathway; – decreased access of tetracycline to the ribosome because of the presence of ribosome protection proteins and

ANTIBIOTICS: SUBCLASSES & EXAMPLES	STRUCTURAL DESCRIPTION AND PROPERTIES	MECHANISM OF ACTION & MODE OF BACTERIAL RESISTANCE DEVELOPMENT
	secretions, including urine and prostate. They accumulate in endothelial cells of liver, spleen, bone marrow, dentine and the enamel of un-erupted teeth. They cross the placenta and enter the foetal circulation and amniotic fluid. Except for doxycycline, the tetracyclines are eliminated renally mainly and also by biliary routes. Doxycycline is not renally eliminated and does not accumulate in renal failure. It is the safest of the tetracyclines in treating extrarenal infections in renally impaired patients. The drug is excreted in the faeces largely as an inactive conjugate or chelate with less impact on intestinal microflora.	– enzymatic inactivation of tetracyclines (Chambers, 2001:1242; Doan *et al.*, 2006:1079)
Glycylcyclines – Tigecycline	Tigecycline is a US- Food and Drug Administration (US-FDA) approved antibiotic. It is a structural analogue of minocycline that was designed to avoid tetracycline resistance mediated by ribosomal protection and drug efflux. Derived from minocycline, it has a tert-butyl-glycylamido side chain added to Carbon 9 of the D ring of the tetracycline nucleus of the parent compound, minocycline (Doan *et al.*, 2006:1081). Doan *et al.*(2006:1101) and Bradford (2004:166) noted these as some of its features: – Broad spectrum of activity – Significant post antibiotic effects at sub-minimum inhibitory concentration against certain pathogens (e.g. *S. pneumoniae* and *E. coli*) – Extensive tissue distribution. This may not allow its use for blood infections	– **Mechanism of action** Bacteriostatic but bactericidal against *S. pneumoniae, H. influenzae* and *N. meningitidis* Tigecycline, like the tetracyclines, binds reversibly to a helical region (H34) on 30S subunit of bacterial chromosomes to block entry of aminoacyl tRNA into the A (acceptor) binding site of the ribosome. Tigecycline in this way inhibits protein synthesis by preventing incorporation of amino acid residues into elongating peptide chains (Doan *et al.*, 2006:1081; Bradford, 2004:164). Tigecycline binding site overlaps with that of the tetracycline on 30 S but the drug avoids tetracycline resistance in bacteria possibly

ANTIBIOTICS: SUBCLASSES & EXAMPLES	STRUCTURAL DESCRIPTION AND PROPERTIES	MECHANISM OF ACTION & MODE OF BACTERIAL RESISTANCE DEVELOPMENT
	– Good penetration into polymorphonuclear neutrophils, alveolar cells and pulmonary epithelial lining fluid, making the antibiotic potentially useful in treating intracellular and respiratory tract infections. – Minimal metabolism in the liver with recovered metabolites being conjugates of glucuronic and acetic acid or epimerization product. Predicted for this reason of non interaction with other drugs through inhibition or induction of cytochrome P450 activities. – Increase in maximum tolerable dose of the drug by food without significant alteration in pharmacokinetics. – Non adjustment of doses in patients with renal impairment, patients on dialysis or patients with mild to moderate hepatic impairment. – It is administered intravenously.	because of: – Its enhanced affinity to the binding site to maintain its antimicrobial potency – Presence of a bulky side chain at C-9 of the tetracycline nucleus provides steric hindrance that prevents efflux proteins from exporting tigecycline out of the cell (Doan *et al.*, 2006:1080). • **Mode of bacterial resistance development** Multidrug efflux systems have been observed as the major contributors to resistance to tigecycline in both gram-positive and gram-negative bacteria.
Macrolides Examples – Erythromycin – Clarithromycin – Azithromycin	Macrolide antibiotics structurally are large molecules containing a many-membered lactone ring to which are attached one or more deoxysugars Erythromycin and clarithromycin have 14-membered rings and azithromycin a 15-membered ring. Clarithromycin differs from erythromycin by methylation of the hydroxyl group at C-6 position of the lactone ring while azithromycin has a methyl substituted nitrogen added to the lactone ring (Chambers, 2001:1250). Essential properties of the macrolides needing consideration in therapy as stated by Chambers (2001:1252,1253)	• **Mechanism of action** – Bacteriostatic but may be bactericidal occasionally – Macrolides bind to 50S ribosomal subunits in domain V of the 23S rRNA and causing premature dissociation of the peptide during translation (Nilius & Ma, 2002:1). – Binding thought to inhibit the translocation step in which a newly synthesized peptidyl tRNA

ANTIBIOTICS: SUBCLASSES & EXAMPLES	STRUCTURAL DESCRIPTION AND PROPERTIES	MECHANISM OF ACTION & MODE OF BACTERIAL RESISTANCE DEVELOPMENT
	and Amsden 2001: S12) are outlined as follows: • Erythromycin: – Absorbed from the duodenum, rather incompletely but adequately. – Inactivated by gastric acid and hence formulated as esters (i.e. stearate, estolate and ethylsuccinate) to improve acid instability and as enteric coated tablets or encapsulated pellets that dissolve in the duodenum. – Food increases gastric acidity and also delays absorption but does not affect bioavailability significantly. – Given intravenously to achieve high plasma concentrations when formulated as the lactobionate or gluceptate. – Diffuses readily into tissues and intracellular fluids, except the brain, to achieve effective antibacterial concentrations. – Achieves concentration of about 50% plasma concentration in middle ear exudate and may not be effective in otitis media caused by *H influenzae* – Crosses placenta barrier to foetal circulation and also appear in breast milk at a significant 50% of plasma concentration. • Clarithromycin: – Rapidly absorbed from the gastrointestinal tract. – Undergoes rapid first pass metabolism to its active metabolite 14-hydroxyclarithromycin. – Both drug and metabolite attain tissue concentrations that are much higher than plasma concentrations.	molecule moves from the acceptor site on the ribosome to the peptidyl site (or donor site) to prevent elongation step in protein synthesis (Chambers, 2001:1251). Anti-inflammatory effects are associated with the macrolides. Mechanisms by which they effect these therapeutic effects include the following: – Degranulation of neutrophils to release upon cell activation microbicidal molecules packed in granules by direct exocytotic effects on human neutrophils – Inhibition of superoxide (O_2^- release in an "oxidative burst" and Ca^{2+} influx into neutrophils. Erythromycin (and also clindamycin inhibited oxidative burst (superoxide formation) and interleukin 8 secretion while azithromycin and on the other hand clarithromycin inhibited oxygen generation and chemotaxis of neutrophils. – Inhibition of synthesis and/or secretion of pro-inflammatory cytokines (Čulić *et al.*, 2001:213) – Inhibition of prostaglandin synthesis by suppressing cytosolic phospholipase A2, cyclooxygenase -1 and -2 mRNA expression (Sata *et al.*, 2007:181)

ANTIBIOTICS: SUBCLASSES & EXAMPLES	STRUCTURAL DESCRIPTION AND PROPERTIES	MECHANISM OF ACTION & MODE OF BACTERIAL RESISTANCE DEVELOPMENT
	– Concentrations of drug and metabolite may be as high as 50% of concentration in plasma. – Standard preparations may or may not be given with food but sustained release formulation of the drug is given with food to improve bioavailability. • Azithromycin: – Absorbed rapidly after oral administration and distributes extensively into all tissues except the cerebrospinal fluid. – Attains tissue and intracellular concentrations (including concentrations in phagocytes) that are much higher than plasma concentrations. The presence of nitrogen in the macrolactone ring structure of the antibiotic becomes protonated in the acid lysosomes of phagocytes. This makes the antibiotic become ion trapped in the cells to account for it's having higher intracellular concentrations than clarithromycin or erythromycin. (Amsden, 2001:S12) – Antacids decrease peak plasma concentrations but not the overall bioavailability. – The antibiotic is not to be administered with food	– Macrolides, are not directly active against *Pseudomonas* but they do reduce secretions of virulence factors of the pathogens e.g. the formation of biofilms that protect the pathogens from antibiotics as seen in people with panbronchiolitis. This may also be the case in the usefulness of the macrolides in treating cystic fibrosis (Ferrara *et al.,* 2005:7) • **Mode of bacterial resistance development** – Resistance to macrolides, lincosamides and streptogramin B (the MLS_B antibiotics) results most commonly from acquisition of erythromycin resistance methylase genes (emr). The genes encode enzymes that methylate 23 S rRNA. – Expression of MLS_B resistance may be constitutive or induced. Macrolides are strong inducers of these enzymes and pathogens may acquire resistance to these antibiotics through this mechanism (Drinkovic *et al.,* 2001: 315). Development of efflux systems by pathogens for extrusion of the antibiotics from the cells (See 2.1.6.1)

ANTIBIOTICS: SUBCLASSES & EXAMPLES	STRUCTURAL DESCRIPTION AND PROPERTIES	MECHANISM OF ACTION & MODE OF BACTERIAL RESISTANCE DEVELOPMENT
Ketolides – Telithromycin	The ketolides are semisynthetic derivatives of erythromycin in which modifications were made to the macrolactone ring to confer improvements in the antimicrobial activity, risks of resistance induction and pharmacokinetics of the ketolides. Such modifications included substitution of the L-cladinose moiety at C-3 with the keto group characteristic of the ketolides. Most ketolides contain a methoxy group at C-6. Telithromycin in addition has a large N-substituted carbamate extension at C-11/C-12 (File, 2005:S363; Nilius & Ma, 2002:4). The keto group and carbamate extensions of the drug molecule bind to domains II and V on the 23S rRNA to increase the binding affinity of the drug to the ribosome subunit to about 10 fold that of erythromycin. This improved contact of telithromycin to the binding site appeared to account for the activity of the antibiotic against macrolide resistant strains of susceptible pathogens (File, 2005: S364; Nilius & Ma, 2002:4). Properties of telithromycin reminiscent to its therapeutic application include the following according to File (2005:S365). – Bioavailability of the antibiotic is not affected by food and the drug can be taken any time without regard to meals. – Maximum serum concentrations are reached one hour after an oral dose – The antibiotic achieves concentration in lower respiratory tract infection sites that are higher than the minimum inhibitory concentrations of common respiratory pathogens – High concentrations of the drugs achieved in sinus tissue after	• **Mechanism of action** Ketolides prevent bacterial protein synthesis in 2 steps. – They interact with 50S ribosomal subunits near the peptidyl transferase sites to inhibit, like the macrolides, the translocation of tRNA to prevent protein elongation. – They also interact with partially assembled 50S subunit precursors to block the formation of functional 50S subunit • **Mode of bacterial resistance development** – No specific mechanism of resistance development to ketolides had been seen to be described for ketolides in the literature – Noted however that ketolides do not induce the enzyme responsible for the most common form of resistance to erythromycin [inducible MLS_B (Macrolide-lincosamide-streptogramin type B phenotype)] and are active against erythromycin resistant strains (Hamilton-Miller & Shah, 2000:941).

ANTIBIOTICS: SUBCLASSES & EXAMPLES	STRUCTURAL DESCRIPTION AND PROPERTIES	MECHANISM OF ACTION & MODE OF BACTERIAL RESISTANCE DEVELOPMENT
	oral administration – Half life of the antibiotic is 10 hours after multiple dosing. Permits once daily dosing. – Ketolides are active against erythromycin resistant strains of pathogenic bacteria (Hamilton-Miller & Shah, 2000:941)	
Lincosamides – Clindamycin – Lincomycin	Clindamycin is a derivative of the amino acid *trans*-L-4-*n*-propylhygrinic acid attached to a sulphur derivative of an octose. It is a congener of lincomycin. Clindamycin, erythromycin and chloramphenicol all bind at sites within close proximity on the 50S subunit of bacterial chromosomes and therefore interact with each other when administered concurrently (Chambers, 2001: 1256.) Macrolide resistance due to ribosomal methylation may cross to clindamycin. The antibiotic does not induce methylase responsible for ribosomal methylation but the induction of the enzymes by the former can cross resistance to the latter by this mechanism. Other properties of therapeutic importance further to Chambers (2001: 1256) include the following: – Complete absorption of the drug following oral administration. – The wide distribution of the antibiotic into tissues including bone, and its significant accumulation in polymorphonuclear leucocytes, alveolar macrophages and abscesses. – The non attainment of significant concentrations of the antibiotic in the cerebrospinal fluid to enable its use in bacterial meningitis. – Drug is mainly eliminated by hepatic route. Dose adjustment required in patients with severe hepatic failure.	• **Mechanism of action** Like the macrolides, the lincosamides bind exclusively to 50S subunit of bacterial ribosomes to suppress protein synthesis. (Chambers, 2001:1156). • **Mode of bacterial resistance development** – Macrolides, lincosamides and streptogramins B have same mechanisms of resistance development that involved methylase induction and consequent .methylation of 23S rRNA (Drinkovic *et al.*, 2001: 315). – Lincosamides (Clindamycin) and streptogramins however are weak inducers of methylase enzymes.

ANTIBIOTICS: SUBCLASSES & EXAMPLES	STRUCTURAL DESCRIPTION AND PROPERTIES	MECHANISM OF ACTION & MODE OF BACTERIAL RESISTANCE DEVELOPMENT
	–	
Quinupristin/Dalfopristin	Combination of streptogramin B (quinupristin) and streptogramin A (dalfopristin) in a 30:70 ratio. They are semisynthetic derivatives of naturally occurring pristinamycins produced by *Streptomyces pristinaespiralis*. The drugs are dissolved in 5% dextrose and administered by IV infusion (The drugs are incompatible with normal saline and have half lives of 0.85 hrs (quinupristin) and 0.7 hrs (dalfopristin). Dosage adjustment not required in renal or hepatic insufficiency.	• **Mechanism of action** Quinupristin binds to 50S ribosomal subunit in the same way as the macrolides, and interferes with protein elongation and hence termination of protein synthesis. Dalfopristinn binds to a site nearby that of quinupristin and induce conformational change of the ribosome. This results in interference with polypeptide formation and also synergistic enhancement of the binding of the quinupristin to its site. • **Mode of bacterial resistance development** – As described for clindamycin
Linezolid	Synthetic antimicrobial agent of oxazolidinone class (Vera-Cabrera *et al.*, 2001:3629). It has 100% bioavailability if orally administered	• **Mechanism of action** Bacteriostatic Binds with 23 S and 50S subunits ribosomal subunits to inhibit protein synthesis by preventing the formation of 70S ribosome, a functional complex which initiates protein synthesis. The drug does not exhibit cross resistance of with other antibiotics. (Chambers, 2001:1260; Vera-Cabrera *et al.*, 2001:3629). • **Mode of bacterial resistance development** – Resistance has been reported clinically only for *S. aureus* (Chambers, 2001:1260)

ANTIBIOTICS: SUBCLASSES & EXAMPLES	STRUCTURAL DESCRIPTION AND PROPERTIES	MECHANISM OF ACTION & MODE OF BACTERIAL RESISTANCE DEVELOPMENT
		Resistance develops as a result of mutation of 23S rRNA on ribosomal binding site (Chambers,2001:1260, Archer & Polk, 2005:794).
C: AGENTS THAT BIND TO 30S RIBOSOMAL SUBUNIT AND ALTER PROTEIN SYNTHESIS LEADING TO ULTIMATE CELL DEATH		
Aminoglycosides – Amikacin – Gentamicin – Netilmicin – Neomycin – Streptomycin – Tobramycin	Structurally aminoglycosides active as antibacterial agents are poly cationic molecules consisting of one or several aminated sugars joined in glycosidic linkages to a dibasic cyclitol which, in the most clinically used of these agents, is a 2-deoxystreptamine (Mingeot-Leclercq *et al.* 1999:727; Galimand *et al.* 2003:2569). The agents are highly polar cations and are very poorly absorbed from the gastrointestinal tract. They are rapidly absorbed from intramuscular sites of injection. Poor perfusion may result in poor absorption from injection sites in the clinically ill patients or patients in shock. Polar nature of the agents precludes their distribution into cell or the cerebrospinal fluid where their concentrations are at subtherapeutic levels. Aminoglycosides cannot be used in treating bacillary meningitis for this reason. The drugs accumulate to high concentrations in the endolymph and perilymph of the inner ear and in the epithelial cells lining the S1 and S2 segments of the nephrons. This characteristic is thought to account for toxicities (nephrotoxicity and ototoxicity) associated with the drugs (Mingeot-Leclercq &Tulkens. 1999: 1003; Chambers, 2001:1225). Characteristics of the aminoglycosides that make them useful antibacterial agents according to (Vakulenko & Mabashery, 2003:430 & 431) include the following:	• **Mechanism of action** The aminoglycoside antibiotics bind to the aminoacyl site (A-site) of 30S ribosomal subunit through the 16S rRNA. This results in impairment of codon-anticodon decoding mechanism and hence the synthesis of aberrant proteins with a consequent blockade of translation fidelity (Wright, 2005:1456; Doi & Arakawa, 2007:88). • **Mode of bacterial resistance development** Most common mechanisms of pathogen resistance development is by means of – enzymatic inactivation of the antibiotics through processes of acetylation and phosphorylation by acetyltransferases and phosphotransferases or transfers to them of nucleotides (adenosine monophosphate) by nucleotidyltransferases, to prevent or reduce their binding to ribosomal subunits (Doi & Arakawa, 2007:88) – Substitution of or methylation of bases involved in the binding between 16S rRNA

ANTIBIOTICS: SUBCLASSES & EXAMPLES	STRUCTURAL DESCRIPTION AND PROPERTIES	MECHANISM OF ACTION & MODE OF BACTERIAL RESISTANCE DEVELOPMENT
	– their concentration dependent bactericidal activity. Killing potential of the aminoglycosides increases with increasing concentration of the antibiotic and is independent of inoculum size. – their postantibiotic effect. Aminoglycosides continue to kill bacteria even after the antibiotic has been removed following a short incubation with the organism. – their relatively predictable pharmacokinetics. Aminoglycosides are dosed on once daily basis to attenuate risks of their nephrotoxic effects. This is made possible on account of their combined postantibiotic effects and their concentration dependent bactericidal activity – their synergism with other antibiotics. Synergistic effects of the aminoglycosides with inhibitors of cell-wall synthesis arise most probably because of enhanced intracellular uptake of the aminoglycosides caused by increased permeability of bacteria after incubation with the cell wall inhibitors.	and the aminoglycoside (Galmand *et al.*, 2003:2565; Doi & Arakawa, 2007:88; Vakulenko & Mobashery, 2003:433) – Decreased cellular uptake of the drug molecules by the bacterial cells by decreasing of permeability bacterial cell membranes to the antibiotic (seen mainly in *Pseudomonas*) Establishing an active drug efflux system for the capture and extrusion of the drug molecules from bacterial cells.
D: AGENTS THAT AFFECT BACTERIAL NUCLEIC ACID SYNTHESIS		
Quinolones/ Fluoroquinolones – Nalidixic acid – Ciprofloxacin – Norfloxacin – Ofloxacin	Quinolones have bicyclic aromatic cores that contain either a carbon or a nitrogen at position 8 to yield respectively true quinolones or ring systems termed naphthyridones (Cross Jr, 2001:211). In usage both the quinolone and naphthyridones compounds according to the author, are referred to as the "quinolones" Antibiotic activity requires the presence of pyridone ring on the right side of the two ring	• **Mechanism of action** Bactericidal Quinolones/fluoroquinolones are direct inhibitors of DNA synthesis. During cell replication, and to accommodate itself within the bacterial cell, an organism's DNA helix is coiled many times and

ANTIBIOTICS: SUBCLASSES & EXAMPLES	STRUCTURAL DESCRIPTION AND PROPERTIES	MECHANISM OF ACTION & MODE OF BACTERIAL RESISTANCE DEVELOPMENT
– Enoxacin` **Advanced generation fluoroquinolones** – Gatifloxacin – Levofloxacin – Moxifloxacin – sparfloxacin	system. Other structural features include a carboxylic acid at C-3 position, a ketone at C-4 and a substituted N at position 1. The name fluoroquinolone comes from the presence of fluorine at C-6. Fluorine is found in all the modern agents. A cyclic diamine (piperazine) moiety is found at C-7 in most of the agents. Newer agents have either amino or methyl substituents at C-5. At C-8 numerous substituents such as fluorine, chlorine and methoxy have been found to improve the potency of the drugs (Cross Jr, 2001:211, Chambers, 2001:1179). Currently used quinolones/fluoroquinolones are classified according to generations of their development according to Jones and Mandell (2002:70) as follows: – **1st generation:** Nalidixic acid and cinoxacin – **2nd generation:** Lomefloxacin, norfloxacin, enoxacin, ofloxacin and ciprofloxacin. [Generally associated with more limited spectrum of activity (some gram-positive and gram-negative aerobic organisms) lower potency, higher frequency of spontaneous bacterial resistance shorter half lives and lower serum drug concentrations (Schaefer, 2003:132)]. – **3rd generation:** Sparfloxacin, gatifloxacin, levofloxacin, moxifloxacin – **4th generation:** Trovafloxacin. Newer generation of fluoroquinolones (3rd and 4th generations) in comparison with the older fluoroquinolones have longer elimination half lives, high bioavailability, high potency, extensive tissue	then twisted in a direction opposite to that of the double helix to create a "negative supercoil" DNA gyrase (topoisomerase II) a tetramer composed of four subunits (2 GyrA and 2 GyrB), catalyses the formation of these negative supercoils and their entry into closed circular chromosomal and plasmid bacterial DNA (Blondeau, 1999:5). This negatively twisted DNA is important for initiation of DNA replication (Cross Jr, 2001:213). Topoisomerase IV, also composed of 4 subunits (2 ParC and 2 ParE), separates interlinked daughter DNA molecules at the terminal end of DNA replication (Chambers, 2001:1179; (Cross Jr, 2001:213). The fluoroquinolones target DNA gyrase (topoisomerase II) and topoisomerase IV. Both targets have different affinities for different quinolones with the former being the main target in gram-negative bacteria and the latter the main target in gram-positive bacteria (Chambers, 2001:1179; Blondeau , 1999: 5; Cross Jr, 2001:213). The drugs bind to the enzyme-DNA complex to stabilize DNA strand breaks created by DNA gyrase. The drug-enzyme-DNA ternary complex block progress of cell replication and ultimate cell death (Li, 2005:454; Dougherty *et al.*,

ANTIBIOTICS: SUBCLASSES & EXAMPLES	STRUCTURAL DESCRIPTION AND PROPERTIES	MECHANISM OF ACTION & MODE OF BACTERIAL RESISTANCE DEVELOPMENT
	penetration and a low incidence of resistance (Schaefer, 2003:132; Blondeau, 1999:19). Fluoroquinolones are well absorbed after oral administration. Food does not impair absorption but do delay time to peak (Blondeau, 1999:19). Concentration of the drugs in urine, kidney, lung, and prostate tissue and also in stool, bile and macrophages is higher than plasma concentration while concentration in cerebrospinal fluid, bone and prostatic fluid are lower than that of serum (Chambers, 2001:1179). Dose adjustment in patients with renal failure may be required for cinoxacin, norfloxacin, ciprofloxacin, ofloxacin, enoxacin and lomefloxacin but not for nalidixic acid, grepafloxacin, trovafloxacin and pefloxacin. Grepafloxacin, trovafloxacin and pefloxacin are eliminated mainly my hepatic metabolism and are not to be used in hepatic failure (Chambers, 2001:1182; Blondeau, 1999:22).	2001:530 &531). • **Mode of bacterial resistance development** Resistance to quinolone occurs through two fundamental mechanisms that involve mutations in bacteria chromosomal genes. These include – Mutations in the GyrA subunit of bacterial DNA gyrase that lower affinity of the drug at the gyrase-DNA complex in both gram-positive and gram-negative organisms (Blondeau, 1999:6). – Mutations of chromosomally encoded drug influx and efflux systems that determine intracellular drug accumulation (Blondeau, 1999:6).
Sulfamethoxazole-Trimethoprim (Co-trimoxazole)	Combined formulation of a sulphonamide (sulfamethoxazole) and a diaminopyrimidine (trimethoprim) an antifolate drug with profound antibacterial activities. Formulation provides optimal ratio concentrations of the two drugs required for synergism and is equivalent to the independent minimal inhibitory concentrations of the two drugs. Most effective ratio for most organisms is 20 parts of sulfamethoxazole to 1 part of trimethoprim.	• **Mechanism of action** – Bactericidal **Sulfamethoxazole**: inhibits the incorporation of para-aminobenzoic acid (PABA) into folic acid in the formation of the compound in bacterial cells. **Trimethoprim**: prevents the reduction of dihydrofolate into tetrahydrofolic. Highly selective for inhibition dihydrofolate for lower organisms. The two agents in their combined formulation provide a two step inhibition of the enzymatic

ANTIBIOTICS: SUBCLASSES & EXAMPLES	STRUCTURAL DESCRIPTION AND PROPERTIES	MECHANISM OF ACTION & MODE OF BACTERIAL RESISTANCE DEVELOPMENT
		pathway involved in the synthesis of tetrahydrofolic acid, resulting in synergistic killing of bacterial cells. Tetrahydrofolic acid is essential for one carbon transfer reactions responsible for the synthesis of nucleosides (e.g. thymidylate) required for bacterial DNA synthesis (Chambers, 2001:1177). • **Mode of bacterial resistance development** Bacterial acquisition of plasmid coding for an altered dihydrofolate reductase. Bacteria resistant to penicillins often resistant to co-trimoxazole. (Chambers, 2001:1177)
Metronidazole	A nitroimidazole chemically identified as 1-(β-hydroxylethyl)-2-methyl-5-nitroimidazole. Completely absorbed following oral administration. Penetrates well into all body tissue and fluids including vaginal secretions, seminal fluids, and saliva and breast milk. Therapeutic concentrations also achieved in the cerebrospinal fluid. The drug does not penetrate the placenta. Mainly undergoes hepatic metabolic elimination. Its hydroxyl metabolite has a longer half life (12 hours) compares to the 8 hour half life of the parent drug and contributes to 50% of the antitrichomonal activity of the metronidazole (Chambers, 2001: 1106)	• **Mechanism of action** – Bactericidal A prodrug that requires metabolic activation for activity. Nitro-group of drug is reduced via metabolic pathways of low redox potential (Land & Johnson, 1999:289). Anaerobic, unlike aerobic organisms, contain electron transport components such as ferredoxins, small Fe-S proteins that have sufficiently negative potential to donate electrons to metronidazole. The single electron transfer

ANTIBIOTICS: SUBCLASSES & EXAMPLES	STRUCTURAL DESCRIPTION AND PROPERTIES	MECHANISM OF ACTION & MODE OF BACTERIAL RESISTANCE DEVELOPMENT
		forms a highly reactive nitro radical anion that kills susceptible organisms by radical formation mediated mechanisms that target DNA (Chambers, 2001:1106). In its prodrug form, metronidazole enters the cell by passive diffusion. Its conversion from inactive to active form leads to further uptake of the inactive drug. This makes the rate of intracellular activation of the drug as important mechanism in the cellular uptake of the drug via a concentration gradient. Aerobic bacteria lack electron transport proteins with sufficiently negative redox potentials and hence are resistant to effects of metronidazole (Land & Johnson, 1999:289). • **Mode of bacterial resistance development** Primary mechanism of drug resistance is lack of drug activation in both protozoa and anaerobic bacteria (Land & Johnson, 1999:292). Molecular mechanisms by which this occurs is not clear for most organisms. Alterations of genes coding for electron donor proteins (rdxA identified in *H. pylori*) have been identified as the main mechanisms by which this occurs in bacteria. Plasmid borne *nim* genes responsible of resistance in *Bacteroides* were suggested to

ANTIBIOTICS: SUBCLASSES & EXAMPLES	STRUCTURAL DESCRIPTION AND PROPERTIES	MECHANISM OF ACTION & MODE OF BACTERIAL RESISTANCE DEVELOPMENT
		encode a 5-nitotrimdazole reductase that could convert 5-nitoimidazoles to a non toxic amino acid derivative (Land & Johnson, 1999:290)

Table 2.9 Spectra of activities of antibiotics and their clinical applications and associated side effects (Compiled from Chambers, 2001:1143 -1266; Archer and Polk &, 2005: 789- 805) and other literature as indicated where such literature had been reviewed)

Antibiotic	Spectra of activity and Therapeutic applications	Associated side effects and drug interactions
β - lactam antibiotics		
Penicillins – Penicillin G – Penicillin V	• **Spectra of activity** Antimicrobial spectra of benzyl penicillin (Penicillin G) and phenoxymethyl penicillin (Penicillin V) are similar. Penicillin G however is 5 to 10 times more active against *Neisseria spp* sensitive to penicillin and against certain anaerobes than Penicillin V. (Chambers, 2001: 1196). Examples of pathogens normally sensitive to the antibiotics include spirochaetes (*Treponema pallidum, Borrelia* and *Leptospira*), aerobic gram-positive cocci, mainly Streptococci spp (excluding enterococci), few staphylococci, *Neisseria* spp, many fastidious oral bacteria (e.g. *Fusobacterium, Porphyromonas Actinomyces*) *Clostridium* spp (except *C. difficile*). Resistance to penicillin is however rapidly emerging among these	• **Adverse effects** Hypersensitivity reactions are by the most common adverse effects noted with penicillins. Skin rashes of all types may be caused by penicillin allergy - scarlatiniform, morbilliform, urticarial, vesicular and bullous eruptions may develop. Purpuric lesions are uncommon. More severe reactions involving the skin, are exfoliative dermatitis, exudative erythema multiforme of either erythematopapular or vesiculobullous type - constitute the

Antibiotic	Spectra of activity and Therapeutic applications	Associated side effects and drug interactions
	pathogens (Archer & Polk , 2005:798) • **Therapeutic applications** Penicillin is the drug of choice for Streptococcal pharyngitis including scarlet fever and also for yaws, syphilis, oral periodontal infections, meningococcal meningitis, Groups A & B streptococcal infections, viridans endocarditis, clostridial myonecrosis, tetanus, anthrax, rat bite fever and Lyme disease (*Borrelia burgdorferi* infections). Enterococcal endocarditis is treated best with a combination of Penicillin G and aminoglycoside. (Archer & Polk, 2005:798; Chambers, 2001:1198)	characteristic Stevens-Johnson syndrome. Administering allopurinol with ampicillin increases the risk (Chambers, 2001:1204)
Penicillinase resistant penicillins – Isoxazolyl penicillins: Oxacillin, Cloxacillin Dicloxacillin – Nafcillin	• **Spectra of activity** *Staphylococcus* spp mainly • **Therapeutic applications** Used solely for treatment of staphylococcal infections caused by susceptible organisms. Nafcillin most effective among the group against infections caused by penicillinase producing strains of *S, aureus.* (Chambers, 2001:1201)	
Aminopenicillins Ampicillin, amoxicillin, and their congeners	• **Spectra of activity** Broad spectrum. As for penicillin in addition to gram-negative bacteria (*E. coli, P. mirabilis, Salmonella* spp, Shigella spp, *Haemophillus influenzae.*) Ampicillin-sulbactam or amoxicillin-clavulanic acid combinations extend the spectra of ampicillin to cover β-lactamase producing *H. influenzae and Enterobacteriaceae.* • **Therapeutic applications** Acute otitis media, meningitis caused by *H. influenzae* & *Listeria*	

Antibiotic	Spectra of activity and Therapeutic applications	Associated side effects and drug interactions
	monocytogenes, meningitis, salmonellosis, *E. faecalis* associated UTI, NB. High rates of resistance of organisms to antibiotic limits its empirical use. Greater than 80% *E. coli* and *P. mirabilis* and > 30% *H. influenzae* resistant are resistant to aminopenicillins. Ampicillin-sulbactam or amoxicillin-clavulanic acid combinations may be used where extend spectra of the ampicillin to cover to β-lactamase producing strains of *H. influenzae and Enterobacteriaceae* (Chambers, 2001:1202; Archer & Polk , 2005:798)	
Cephalosporins 1st Generation – Cefazolin – Cephalothin – Cephalexin – Cephradine – Cefadroxil	• **Spectra of activity** Spectra of activity of the 1st generation cephalosporins cover mainly streptococci except for penicillin resistant strains and also *Staphylococcus aureus* in the exception of methicillin resistant strains. They have excellent activity against many isolates of *E. coli, Klebsiella pneumoniae* and *P. mirabilis*. (Archer & Polk, 2005: 798, Chambers, 2001: 1209) • **Therapeutic applications** May be used when infections of gram-positive bacteria are suspected but they are not the drugs of choice. They are drugs of choice in the presumptive treatment of community acquired urinary tract infections. (Archer & Polk, 2005: 798. They are excellent agents for skin and soft tissue infections due to *S. aureus* and *S, pyogenes*. Single dose of cefazolin just before surgery is preferred prophylaxis for procedures in which skin flora are the likely pathogens.	• **Adverse effects** – Most common side effects include hypersensitivity reactions identical to those seen with the penicillins. Immediate reactions such as anaphylaxis, bronchospasm and urticaria are observed. – Cephalosporins are implicated in nephrotoxic episodes. Cephaloridine in dose higher than 4g per day and also high doses of cephalothin may cause renal tubular necrosis. Concurrent. administration of cephalothin and gentamicin or tobramycin may act synergistically to cause nephrotoxicity. – Diarrhoea can result from administration of

Antibiotic	Spectra of activity and Therapeutic applications	Associated side effects and drug interactions
	(Chambers, 2001:1213)	cephalosporins and may be more frequent with cefoperazone. – Intolerance to alcohol has been noticed with the cephalosporins (a disulfiram reaction) that contain methyl-tetrazole-thio-methyl group (MTT) at C-3 of the cephem nucleus (Cefamandole, cefonid, cefotetan, cefoperazone and moxalactam). – Serious bleeding related either to hypoprothrombinaemia due to MTT group platelet dysfunction (Chambers, 2001:1212).
2nd Generation – Cefamandole – Cefoxitin (cephamycin) – Cefotetan (cephamycin) – Cefuroxime – Cefaclor – Cefotetan – Cefditoren – Cefdinir	• **Spectra of activity** Cefuroxime and cefaclor have useful activity against *E. coli, Klebsiella, Proteus, H. influenzae* and *Moraxella catarrhalis*. Not as active against gram-positive organisms as the first generation agents Cefoxitin and cefotetan have inferior activity against *S. aureus* in comparison with cefuroxime but with added activity against *Bacteroides fragilis* and other *Bacteroides* (Chambers, 2001:1209) • **Therapeutic applications** Cefoxitin or cefotetan are preferred in prophylaxis in colorectal surgery where intestinal anaerobes are involved. For intra abdominal infections, pelvic inflammatory disease and diabetic foot where facultative gram-negative bacilli and anaerobes are involved, cefotetan and cefoxitin have been shown to be effective.	
3rd Generation – Cefotaxime – Ceftriaxone – Ceftazidime – Cefoperazone – Cefpodoxime (oral) – Cefixime (oral)	• **Spectra of activity** *Enterobacteriaceae, Serratia, Neisseria gonorrhoea, S. aureus, Streptococci* and *S. pyogenes.* Ceftazidime only is effective against *Pseudomonas aeruginosa* and lack significant activity against gram-positive cocci. • **Therapeutic applications** Drugs of choice for serious infections caused by *Klebsiella, Enterobacter, Proteus, Providencia, Serratia* and *Haemophilus* spp	

Antibiotic	Spectra of activity and Therapeutic applications	Associated side effects and drug interactions
	Ceftriaxone now therapy of choice for all forms of gonorrhoea and for severe forms of Lyme disease Ceftriaxone or cefotaxime in 3-drug combination with vancomycin and ampicillin are used in initial treatment of meningitis in nonimmunocompromised adults and children older than 3-months because of their antimicrobial activity penetration into the central nervous system (CNS). They are also the drugs of choice for the treatment of meningitis caused by *H. influenzae, N. meningitidis,* and sensitive *S. pneumoniae* and gram-negative enteric bacteria. Cefotaxime and ceftriaxone are also excellent for the treatment of community acquired pneumonia caused by pneumococci (Chambers, 2001:1213; Archer & Polk, 2005: 798).	
4th Generation – Cefepime – Cefpirome	• **Spectra of activity** Cefepime has a spectrum comparable to the 3rd generation but is more resistant to some β-lactamases. • **Therapeutic applications** 4th generation cephalosporins are indicated for he empiric treatment nosocomial infections where antibiotic resistance due to ESBLs or chromosomally induced β-lactamases are anticipated. Cefepime has superior activity against nosocomial isolates of *Enterobacter*, *Citrobacter* and *Serratia* spp compared to ceftazidime and piperacillin (Chambers, 2001:1213).	
Penems **Carbapenems**	• **Spectra of activity** The penems have the broadest antibacterial spectrum of any β-	• **Adverse effects** Nausea and vomiting are the most common

Antibiotic	Spectra of activity and Therapeutic applications	Associated side effects and drug interactions
– Imipenem – Meropenem – Ertapenem – Doripenem **Penems** – Faropenem	lactam antibiotic. Among gram-positive organisms, they demonstrate activity against *S. aureus, Streptococcus pneumoniae, including penicillin resistant strains, StreptococcuS. pyogenes, Listeria monocytogenes and Enterococcus faecalis*, Meropenem is less active than imipenem against gram-positive cocci. Among gram-negative organisms they are active against gram-negative respiratory pathogens including *H. influenzae* (both β-lactamase producing or non-producing strains) and also against gram-negative bacilli including *Pseudomonas.* They are remarkably stable against β-lactamases, including type-1-inducible β-lactamases responsible for 3rd generation cephalosporin-resistant strains of *Enterobacter, Serratia, Citrobacter* and *Pseudomonas.* They exhibit synergistic activities against gram-negative bacilli when combined with aminoglycosides (Darville, 1999:38 &39). The penems are inactive against *Stenotrophomonas maltophilia*, *Enterococcus faecium* and intracellular organism such as rickettsiae, mycoplasma, ureaplasma and chlamydiae (Darville, 1999:38). • **Therapeutic applications** Imipenem/cilastatin is indicated for treatment of patients 12 years and older for a variety of wide serious infections caused by a broad spectrum of gram-positive and gram-negative organisms and many anaerobes. Indicated mainly are such conditions as bacteraemia, endocarditis, intraabdominal and gynaecologic infections and infections of the lower respiratory tract, urinary tract, bone and	side effects of the penems. Seizures are induced in about 1.5% of cases particularly in patients receiving high dose for CNS lesions (Chambers, 2001:1214). The excitatory potential and hence their ability to induce seizures is in the order of imipenem > meropenem > doripenem. Faropenem has very low excitatory potential (Dalhoff *et al.*, 2006:1088**).** Laboratory abnormalities associated with drugs include thrombocytosis, eosinophilia and changes in hepatic enzymes (Darville, 1999:40). Drug - drug interactions seen with the carbapenems include the reduction of plasma levels of the antiepileptic drug valproic acid by panipenem. The interaction has not been reported for imipenem and meropenem (Knapp & English, 2001:180).

Antibiotic	Spectra of activity and Therapeutic applications	Associated side effects and drug interactions
	joints, and skin and soft tissues (Knapp & English, 2001:181). The antibiotic is not approved for meningitis because safety and efficacy had not been established (Knapp & English, 2001:181). Meropenem approved for use in both adults and children as single agent therapy for intraabdominal infections and for bacterial meningitis. Carbapenems have antipseudomonal activity but should be used with caution in pseudomonal infections. Imipenem/cilastatin e.g. should not be used alone in pulmonary exacerbations in cystic fibrosis because of risks of treatment failure and emergence of *Pseudomonas* resistant strains. *Pseudomonas* isolates may develop resistance during carbapenem therapy which could result in treatment failure (Knapp & English, 2001:181).	
Aztreonam	• **Spectra of activity** Antimicrobial activity of Aztreonam resembles those of the aminoglycosides rather than other β-lactam antibiotics. Gram-positive bacteria and anaerobic bacteria are resistant. It has excellent activity against *Enterobacteriaceae* and *P. aeruginosa*, *H. influenzae* and *Neisseria* spp. (Chambers, 2001:1214) • **Therapeutic applications** Aztreonam is used for therapy of various infections caused by gram-negative bacteria. It does not seem to demonstrate cross allergic reactions seen with penicillins and cephalosporins and is thus usefully employed in treating penicillin sensitive patients for gram-negative infections (Chambers, 2001:1214).	
Glycopeptides	• **Spectra of activity**	• **Adverse effects**

Antibiotic	Spectra of activity and Therapeutic applications	Associated side effects and drug interactions
– Vancomycin – Teicoplanin	Primarily active against gram-positive bacteria. Susceptible strains include *Staphylococcus aureus, Staphylococcus epidermidis* including strains resistant to methicillin. *S. pyogenes* and *S. pneumo*niae and viridans streptococci are highly susceptible to vancomycin. Enterococci were once uniformly sensitive but resistant strains of *Enterococcus faecium* have emerged as major nosocomial pathogens (Archer & Polk, 2005:799). • **Therapeutic applications** Vancomycin is employed in treating serious infections due particularly to methicillin resistant infections, including pneumonia, empyema, endocarditis, osteomyelitis, and skin and soft tissue abscesses and in severe staphylococcal infections in patients who are allergic to the penicillins and cephalosporins (Chambers, 2001:1264, Archer & Polk, 2005: 799).	Vancomycin may cause hypersensitivity reactions. With macular skin rashes and anaphylaxis. Rapid iv infusion may cause a lot of symptoms including erythematous or urticarial reactions, flushing, tachycardia, and hypotension. Ototoxicity and nephrotoxicity may be associated with high doses of the drug. Caution must be taken when given concurrently with ototoxic and nephrotoxic drugs e.g. aminoglycosides or in patients with renal insufficiency (Chambers, 2001:1264).
Chloramphenicol	Has broad activity against gram-positive and gram-negative bacteria including • **Spectra of activity** Streptococci (*S. pyogenes, S. pneumoniae, S. agalactiae*), *H. influenzae, N. meningitidis, N. gonorrhoeae, Brucella spp. Bordetella pertussis*, anaerobic bacteria including gram-positive cocci and *Clostridia* spp, and gram-negative rods including *B. fragilis*. *Staphylococcus* is less susceptible. Susceptibility of *Enterobacteriaceae* is variable with most strains of *E. coli* and *Klebsiella* being susceptible. Approximately 50% of *Proteus mirabilis* and indole positive *Proteus* spp are susceptible. *P. aeruginosa* is very resistant to Chloramphenicol. *V. cholerae* remained largely	• **Adverse effects** Chloramphenicol inhibits synthesis of mitochondrial proteins which may account for much of the toxicity associated with the antibiotic. ° Hypersensitivity reactions - uncommon. May show as macular or vesicular skin rashes. ° Haematological reactions: – Suppression of haematopoietic system resulting in anaemia, leukopenia or thrombocytopenia

Antibiotic	Spectra of activity and Therapeutic applications	Associated side effects and drug interactions
	susceptible. Strains of *Shigella* and *Salmonella* resistance to multiple drugs including chloramphenicol are on the rise. *Chlamydiae*, *Mycoplasma* and *Rickettsiae* are also sensitive • **Therapeutic applications** Therapy with chloramphenicol is limited to infections for which the benefits of the drug outweigh the risks of its potential toxicities. It should never be used in undefined situations or in diseases readily, safely, and effectively treatable with other antimicrobial agents (Chambers, 2001: 1248). Its indications include : **Typhoid fever**: Responses more rapid with oral dosage formulations. Third generation cephalosporins and quinolones are drugs of choice. **Bacterial meningitis**: Chloramphenicol is effective but is used as an alternative choice to 3rd generation cephalosporins in meningitis caused by *H. influenzae*, *N. meningitidis* and *S pneumoniae*. Results of chloramphenicol treatment of *S pneumoniae* meningitis are unsatisfactory because some strains are inhibited but not killed. **Anaerobic infections**: Chloramphenicol is quite effective in most anaerobic infections including intraabdominal infections but the antibiotic is rarely indicated for these infections because of its toxicity and the availability of equally effective drugs. **Rickettsial diseases**: Chloramphenicol may only be antibiotic of choice instead of tetracycline for rickettsial diseases in the following patient groups: Patients sensitised to the tetracyclines; patients with reduced renal function; pregnant women, children less than 8 years of age and	Idiosyncratic response manifesting as aplastic anaemia leading to fatal pancytopenia. Aplastic anaemia occurs more with oral than parenteral dosage forms. – Erythroid suppression of the bone marrow. Results from impairment of iron incorporation into erythrocytes due to inhibitory action of the drug on mitochondrial protein synthesis. ° Gray syndrome - fatal chloramphenicol toxicity in neonates - failure of the drug to be conjugated with glucuronic acid owing to inadequate activity of glucuronyl transferase in the liver at that time of life . (Chambers, 2001: 1248).

Antibiotic	Spectra of activity and Therapeutic applications	Associated side effects and drug interactions
	certain patients who require parenteral formulations because of severe illness (Chambers, 2001: 1248).	
Tetracyclines Examples: – Tetracycline – Chlortetracycline – Demeclocycline – Oxytetracycline – Tetracycline – Doxycycline – Minocycline	• **Spectra of activity** Tetracyclines are active against a wide range of aerobic and anaerobic gram-positive and gram-negative bacteria but generally more active against gram-positive than gram-negative bacteria. Cross resistance features prominently among the various drugs in the grouping. Activity levels in accordance with Chambers, 2001:1240 cover mainly *Streptococcus pneumoniae*. *Staphylococcus aureus* is sensitive to about 65% and Group B Streptococci (*S. agalactiae*) only 50%. *H. influenzae* is about 90% sensitive and most strains of *Brucella* are susceptible. They are particularly useful in infections caused by *H. ducreyi* (chancroid), *Brucella* and *Vibrio cholerae*. *N. gonorrhoea* and *N. meningitidis* are now generally resistant to the tetracyclines. They are also active against many anaerobic organisms including *Bacteroides* spp. Doxycycline is much less active against *B. fragilis* than is chloramphenicol, clindamycin, metronidazole and certain β-lactam antibiotics. Among the gram-positive anaerobic organisms, *Propionibacterium* is most and *Peptococcus* the least sensitive to the tetracycline. The class of antibiotics are also active against spirochaetes including *Borrelia recurrentis*, *B. burgdorferi* (Lyme disease), *Treponema pallidum* and *Treponema pertenue*. They are also active against bacteria resistant to cell wall active antimicrobial agents such as *Rickettsia, Coxiella burnetti, Ureaplasma, Mycoplasma pneumoniae* ,*Legionella* spp *Chlamydia* spp, some	• **Adverse effects** Common adverse effects associated with the tetracyclines as indicated by Archer and Polk (2005:802) and Chambers (2002:1245) include the following: – Gastrointestinal irritation. Associated with all tetracyclines in some individuals and may show as epigastric burning and distress, abdominal discomfort, nausea and vomiting. – Administration of the drugs with food reduces the incidence of gastric discomfort. – Photosensitivity of the skin to sunlight: Demeclocycline and doxycycline are mostly implicated – Hepatic toxicity: May develop when doses of 2 g or greater are given parent rally or when larger doses are given orally. Pregnant women appear mostly susceptible. Oxytetracycline and tetracycline are the least hepatotoxic among the agents. – Renal toxicity: the drugs aggravate uraemia in patients with renal disease. They block protein synthesis and provoke catabolic effects. Doxycycline has the least renal

Antibiotic	Spectra of activity and Therapeutic applications	Associated side effects and drug interactions
	atypical mycobacteria and plasmodium • **Therapeutic applications** Chambers (2001:1243,1244) and other authors as indicated cited the following as some uses of the tetracyclines: – Treatment of infections caused by rickettsiae, mycoplasmas and chlamydiae. – Brucellosis (*Brucella melitensis, B. suis,* and *B. abortus*) where doxycycline is combined with rifampicin by World Health Organisation recommendations for such treatment (Corbel & Beeching, 2005:917). – Cholera (some strains of *V. cholerae* now known to be resistant). – Community acquired pneumonia: Doxycycline where remains an effective empiric therapy because of about 85% of S. pneumoniae still being susceptible to the tetracyclines (Ailani *et al.*, 1999:266). Yaws (*Treponema pallidum*), relapsing fever (*Borrelia recurrentis*) and Lyme disease (*B. burgdorferi*) respond well to tetracyclines.	effects. Nephrogenic diabetic insipidus may be seen in patients receiving demeclocycline – Permanent teeth discolouration: most common in children of ages 2 months to 5 years or children born of pregnant women given the drugs. Caused by the formation and deposition of tetracycline-calcium orthophosphate complexes in the teeth during its development. – Tetracyclines are deposited in the skeleton during gestation and through out child hood. This may cause depression of bone growth. – Long term therapy with tetracyclines may cause changes in peripheral blood with leukocytosis, atypical lymphocytes, toxic granulation of granulocytes and thrombocytopenia as main features.
Glycylcyclines – Tigecycline	• **Spectra of activity** Tigecycline has a broad spectrum of activity against gram-positive and gram-negative bacteria and anaerobes including many multidrug-resistant bacteria notably methicillin resistant *S. aureus* (MRSA), vancomycin resistant enterococci (VRE), penicillin resistant *S. pneumoniae*, and extended β-lactamase (ESBL) or *Amp*C β-lactamase-producing *Enterobacteriaceae* (Doan *et al.*, 2006:1101). Tigecycline does not have reliable activity against *P.*	• **Adverse effects** Most reported adverse effects of tigecycline documented by Doan (2006:1097) include nausea, vomiting, diarrhoea, local reaction at IV site, abdominal pain and headache. Mild laboratory abnormalities were also reported and included lymphopenia, thrombocytopenia, hypokalaemia and hypophosphatemia. Adults

Antibiotic	Spectra of activity and Therapeutic applications	Associated side effects and drug interactions
	aeruginosa and members of the indole positive Proteae (i.e. *Proteus vulgaris, Morganella* spp, and *Providencia* spp (Doan *et al.*, 2006:1101; Bradford, 2004:163,164) • **Therapeutic applications** Indicated for the treatment of complicated skin and skin structure infections and complicated intraabdominal infections caused by susceptible strains of bacteria in patients 18 years and above. (Doan 2006:1080). It is considered a good choice for the treatment of polymicrobial surgical wound infections after abdominal surgery, in which MRSA, anaerobes and Enterobacteriaceae are the most likely pathogens. The antibiotic also have a role in the treatment of infections caused by ESBL- or *Amp*C β-lactamase -producing *Enterobacteriaceae* in patients who are allergic to or unable to tolerate carbapenems (Doan *et al.*, 2006:1101).	between the ages of 18 and 50 years and women appear to be at greatest risk of nausea and vomiting side effects of the drug. Co-administering the drug with food improves its tolerability with fewer incidences of nausea and vomiting.
Macrolides Examples – Erythromycin – Clarithromycin – Azithromycin	• **Spectra of activity** Erythromycin is active against aerobic gram-positive cocci and bacilli including susceptible strains of *Streptococci pyogenes* and *S. pneumoniae, Clostridium perfringens, Corynebacterium diphtheriae* and *Listeria monocytogenes*. It is also active against *Legionella, Mycoplasma, Campylobacter, Bordetella pertussis* and some *Chlamydia* (e.g. *Chlamydia trachomatis*). It has modest activity against some gram-negative bacteria including *H. influenzae, N. meningitidis* and good activity against *N. gonorrhoea* (Archer & Polk 2005: 799; Chambers, 2001:1251). Of importance in pathogen resistance to erythromycin, Chambers (2001:1251) noted the	• **Adverse effects** Majority of side effects of macrolides as indicated in (Williams, 2001:S77) include the following: – Gastrointestinal tract side effects including abdominal pain, nausea, vomiting and/or diarrhoea. Administration of the drug with food ameliorates these side effects to some extent (Sabella & Goldfarb, 1999:10). – Hepatotoxicity: Associated with erythromycin esters with the estolate being linked with the

Antibiotic	Spectra of activity and Therapeutic applications	Associated side effects and drug interactions
	following: – mechanisms producing resistance against erythromycin affect all macrolides. – macrolide resistance among *S. pneumoniae* are associated with penicillin resistance. – there is complete cross resistance within the macrolide antibiotics. – erythromycin is not active against enteric gram-negative bacilli. Clarithromycin has good activity against *M. catarrhalis, Mycoplasma pneumoniae, Chlamydia spp. L. pneumophila,* and *B. burgdorferi* (Chambers, 2001:1251) and additionally against *S. pneumoniae*, *StreptococcuS. pyogenes*, *H. influenzae* and *H. parainfluenzae* as further reported by Anzueto and Norris, (2004:2). Azithromycin is very active against *M. catarrhalis, M. pneumoniae, Chlamydia spp, Pasteurella multocida. L. pneumophila, B. burgdorferi, Fusobacterium spp* and *N. gonorrhoea*. It is less active than erythromycin against gram-positive organisms (*Streptococcus* spp including enterococci) but more active than erythromycin and clarithromycin against *H. influenzae and Campylobacter* spp (Chambers, 2001:1251). • **Therapeutic applications** The macrolides are indicated mainly in the treatment of community acquired pneumonia, acute exacerbation of chronic bronchitis, acute bacterial sinusitis and pharyngitis (Anzueto & Norris, 2004: S7 - 11). They are also shown to have anti-inflammatory properties (Anzueto	development of cholestatic hepatitis. – Side effects are dose related and reduce with continuous or long term use. They are twice as less frequent for clarithromycin as they are for erythromycin and even far less frequent for azithromycin and the 16 membered rings (e.g. josamycin) (Williams, 2001:S77). – Erythromycin, clarithromycin azithromycin and dirithromycin have all been reported to provoke excessive prolongation of QT interval (Justo *et al.*, 2004:326). – Macrolides are extensively metabolised in the liver and competitively interfere with the hepatic metabolism of drugs by cytochrome P450. This can result in the accumulation of co-administered drugs such as theophylline, carbamazepine, cyclosporin and warfarin. The interaction occurs less frequently with azithromycin (Sabella & Goldfarb, 1999:10).

Antibiotic	Spectra of activity and Therapeutic applications	Associated side effects and drug interactions
	& Norris, 2004:S12; Ferrara *et al.*, 2004:8; Giamarellos-Bourboulis, 2008:18). According to Anzueto and Norris (2004:S12), their use in the treatment of inflammatory pulmonary diseases such as chronic sinusitis , chronic obstructive airways disease and asthma were seen to improve symptoms associated with these conditions even in absence of bacterial infections. In asthma they were seen to decrease hyper-responsiveness and steroid usage with improvement of symptoms. They also improve bronchial and nasal mucous secretions clearance and sputum purulence. Clinical trials of their use in cystic fibrosis also suggested the potential beneficial use of the agents in managing this condition. (Ferrara *et al.*, 2005: 10). Pending results of clinical trials conducted to establish beneficial effects of the long term use of the macrolides in treating bronchial asthma, chronic obstructive airways disease and bronchiectasis, the exact role of the drugs in everyday clinical practice for the therapy of chronic respiratory conditions cannot be defined (Giamarellos-Bourboulis, 2008:18). Studies have also shown that long term use of the macrolides carries risks of acquisition of resistance by normal flora. This according to Giamarellos-Bourboulis (2008:18) is a dilemma in the use of the antibiotics solely for their anti-inflammatory effects.	
Ketolides – Telithromycin	• **Spectra of activity** Telithromycin is active against many common gram-positive and	• **Adverse effects** File (2005:369) documented the following as

Antibiotic	Spectra of activity and Therapeutic applications	Associated side effects and drug interactions
	gram-negative organisms, as well as atypical and intracellular respiratory pathogens including MLS_B-resistant strains and specifically *S. pneumoniae* strains that express either erm or mef genes, both β-lactamase -negative and β-lactamase producing strains *H. influenzae*, atypical respiratory pathogens i.e. *Bordetella*, *Legionella* spp, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*. Telithromycin is essentially inactive against Enterobacteriaceae, non-fermentative gram-negative bacilli, *Acinetobacter baumannii*, and constitutively MLS_B - resistant *S. aureus* (File, 2005:S366). • **Therapeutic applications** Evaluations of the clinical effectiveness of telithromycin according to File (2005:S367 -368) showed the antibiotic to be effective in treating community acquired respiratory tract infections including: – mild to moderate community acquired pneumonia; – acute exacerbation of bronchitis; and – acute bacterial sinusitis. Telithromycin has activity against the most common typical and atypical respiratory tract infections, including penicillin and macrolide resistant strains. It has the potential for first line treatment option for community acquired respiratory tract infections, particularly in patients at risk for infection with antibiotic resistant strains (File, 2005:368).	adverse effects associated with telithromycin use. – Treatment emergent adverse effects: Gastrointestinal discomfort mainly was reported – Exacerbations of myasthenia gravis during treatment with telithromycin. – Prolongation of QTc interval of the electrocardiogram. – Mild to moderate transient visual disturbances. – Telithromycin causes inhibition of the drug metabolising enzyme CYP3A4 and cause increased concentrations of drugs administered concurrently with it. Increase in plasma concentration of simvastatin administered concurrently with telithromycin is documented.

Antibiotic	Spectra of activity and Therapeutic applications	Associated side effects and drug interactions
Lincosamides – Clindamycin – Lincomycin	• **Spectra of activity** Chambers (2001:1257) made the following notations on the spectra of activity for clindamycin – Similar to erythromycin in its activity against susceptible strains of *Streptococcus pneumococci, StreptococcuS. pyogenes* , and viridans streptococci. – More active than erythromycin or clarithromycin against anaerobic bacteria particularly *B. fragilis* and also *B. melaninogenicus*, *Fusobacterium*, (*Fusobacterium varium* are resistant) *Peptostreptococcus, Peptococcus and Clostridium perfringens* (other clostridium species resistant). – All aerobic gram-negative bacilli are resistant. – Clindamycin has some activity against *Plasmodium falciparum* and *P. vivax*.) • **Therapeutic uses** – Drug of choice in the treatment of severe invasive infections group A streptococci (*S. pyogenes*) infections. Not indicated for facultative gram-negative bacilli like erythromycin (Archer & Polk, 2005:799). Chambers (2001:1257) noted additionally the following as valuable therapeutic uses of clindamycin. They include: – Treatment of infections due to anaerobes particularly *B fragilis.* It has been used successfully with an aminoglycoside for infection resulting from faecal spillage. – Based on some study results, which still are being debated, clindamycin instead of penicillin has become the antibiotic of	• **Adverse effects** Chambers 2001:1257 and Archer and Polk (2005:802) both indicated the following as most common adverse effects reported with the use of clindamycin. – Gastrointestinal distress with diarrhoea and pseudomembranous colitis being reported at respective rates of rates of up to 20% and 10% of cases . Metronidazole is effective in treating symptomatic patients with pseudomembranous colitis. – Allergic reactions, in form of skin rashes, and fever and also hepatotoxicity and neutropenia are reported but rarely. – Clindamycin can inhibit neuromuscular transmission and hence can potentiate the effects of neuromuscular blocking agents when concurrently administered with these drugs.

Antibiotic	Spectra of activity and Therapeutic applications	Associated side effects and drug interactions
	choice in treating, lung abscess and anaerobic lung and pleural space infections. – It has also been shown to be effective in treating encephalitis caused by *T.* gondii in AIDS patients. It is also useful when used in combination with primaquine in treating mild to moderate case of *Pneumocystis carinii* pneumonia in same category of patients. – Formulated as topical solutions, lotions or gels and vaginal creams clindamycin is also effective topically in treating acne vulgaris and bacterial vaginosis.	
Quinupristin/Dalfopristin	• **Spectrum of activity** The spectrum of activity of streptogramins is limited to gram-positive bacteria including *Streptococcus pneumoniae*, streptococci and *E. faecium* but not *E. faecalis* (Archer & Polk, 2005:800, Chambers, 2001:1258). Quinupristin and Dalfopristin are highly inactive against gram-negative bacteria except *Moraxella catarrhalis* and *Neisseria* spp which are susceptible (Chambers, 2001:1258). • **Therapeutic uses** Indicated for the treatment of infections caused by staphylococci both methicillin susceptible and methicillin resistant strains of *Staphylococcus aureus.* , streptococci and *E. faecium*. (It is not active against *E. faecalis*).	• **Adverse effects** Commonly associated side effects according to Chambers (2001:1259) include the following: – Pain and phlebitis at site of infusion (can be avoided by using central venous lines and – arthralgias and myalgias. Streptogramins inhibit cytochrome P450 enzyme 3A4 (CyPA4). The following drugs that are metabolised by this enzyme and thus would have plasma concentration level increases include: terfenadine, astemizole, indinavir, nevirapine, midazolam, nifedipine and other calcium channel blockers and cyclosporin.
Linezolid	• **Spectrum of activity** Primary activity of linezolid is against gram-positive organisms. The agent has a very wide spectrum of activity including its activity	Linezolid is well tolerated. Reported minor side effects occurring at rates equal to that of comparator agents include,

Antibiotic	Spectra of activity and Therapeutic applications	Associated side effects and drug interactions
	against vancomycin resistant *E. faecalis* and *E. faecium*, methicillin-resistant *S. aureus*, anaerobes, mycobacteria and other gram-positive organisms (Vera-Cabrera *et al.*, 2001:3629). • **Therapeutic applications** Mainly used for infections caused by vancomycin resistant *E. faecium*, nosocomial pneumonias caused by methicillin susceptible and methicillin resistant *S. aureus*, community acquired pneumonia caused by penicillin susceptible *Streptococcus pneumoniae*, Complicated skin and soft tissue infections caused by streptococci and methicillin susceptible and methicillin resistant *S. aureus* (Chambers, 2001:1260).	– gastrointestinal complaints headache and rash; – thrombocytopenia with incidences of occurrence related to length of use the drug; and – weak monoamine oxidase inhibiting effect. May enhance effects of adrenergic or serotogenic agents when used concurrently with such agents.
Aminoglycosides – Amikacin – Gentamicin – Netilmicin – Neomycin – Kanamycin – Streptomycin – Tobramycin	• **Spectra of activity** Antibacterial activity of the aminoglycosides covers mainly aerobic gram-negative bacilli including Enterobacteriaceae (*E. coli, Klebsiella, Proteus spp, Salmonella spp, Shigella*) *Pseudomonas, Enterobacter spp, Citrobacter, Acinetobacter, Serratia, Morganella spp* (Vakulenko & Mabashery, 2003:430) They have little and limited activity respectively against *Bacteroides* spp and other anaerobic and gram-positive organisms. They are not effective in environments that are acidic or have low oxygen tension. *Streptococcus pneumoniae* and *StreptococcuS. pyogenes* are resistant (Chambers, 2001: 1223; Archer & Polk, 2005:799.). Their activity against enterococci is adequate only when they are used synergistically with a cell wall-active antibiotic, such as β-lactam antibiotics or vancomycin (Vakulenko & Mabashery, 2003:430).	• **Adverse effects** Main adverse effects of the aminoglycosides include ototoxicity and nephrotoxicity. ○ **Ototoxicity**: The toxicity is irreversible. – Both vestibular and auditory dysfunction can follow aminoglycoside administration due to progressive accumulation of the drugs in the endolymph and perilymph (Chambers, 2001:1227). – Associated mainly with persistent high plasma levels of the drugs but it is also known that plasma concentrations of the drugs at therapeutic ranges can also result in rapid, profound and irreversible hearing

Antibiotic	Spectra of activity and Therapeutic applications	Associated side effects and drug interactions
	Newer aminoglycosides such as gentamicin, tobramycin, amikacin Netilmicin, isepamycin, dibekacin and arbekacin have broader spectra of activity than the older agents, streptomycin and kanamycin. On account of their limited spectra of activity these are not to be used in treating *Pseudomonas* and *Serratia* infections. Tobramycin has superior activity than gentamicin against *Pseudomonas aeruginosa* (Chambers, 2001:1223). Arbekacin, a widely used aminoglycoside in Japan, demonstrates the widest spectrum of antibacterial activity. It has very good activity against methicillin resistant *Staphylococcus aureus* (Vakulenko & Mabashery, 2003:430). Tobramycin and gentamicin have up to 90% and 75% activity against *Staphylococcus aureus* and *Staphylococcus epidermidis.* Gentamicin is however not to be used alone in treating staphylococci infections on account of the rapid emergence of gentamicin-resistant mutants of the pathogens during their exposure to the antibiotic. Also staphylococcal resistance mediated by conjugative plasmids that code for aminoglycoside-modifying enzymes is common among methicillin resistant strains of staphylococci. (Chambers, 2001:1224). • **Therapeutic applications** The following are listed by Chambers (2001:1231 - 1235) and Archer and Polk (2005:799) as infections in which aminoglycosides are most commonly used. – Frequently used (often in combination with penicillins and cephalosporins) for infections - proven or suspected - of gram-negative microbial infections. Their uses however are greatly	loss in some individuals (Bitner-Glindzicz & Rahman, 2007:784). – Genetic predisposition to the development of the adverse effect associated with mutations in mitochondrial DNA in some individuals, has also been established. It is now known to account for at least 33%-59% of aminoglycoside ototoxicity (Bitner-Glindzicz & Rahman, 2007:784). – Aminoglycosides catalyse the formation of free radicals in an iron dependent reaction which are implicated in the development of ototoxicity. Substances including salicylates, aspirin and antioxidants which either chelate iron or act as antioxidants have been shown by a number of studies to attenuate aminoglycoside-induced ototoxicity (Schacht, 1999: 125; Sha and Schacht, 1999:807; Chen *et al.*, 2007:178). ° **Nephrotoxicity**: The toxicity is reversible. – Caused by accumulation and retention of aminoglycosides in proximal tubular cells. – Demonstrates as defect in renal concentration of urine, appearance of hyaline granular casts in the urine, mild proteinuria and reduction in glomerular

Antibiotic	Spectra of activity and Therapeutic applications	Associated side effects and drug interactions
	limited by their renal and otic toxic effects. Their specific indications include. ° **Urinary tract infections** (UTI): A single intramuscular dose of gentamicin is about 90% effective in uncomplicated UTI but neither the antibiotic nor other aminoglycosides are indicated for such these infections. They are indicated in severe infections of the upper urinary tract e.g. pyelonephritis either alone or in combination with β-lactam antibiotics for initial treatment. They should be discontinued in such treatment if infecting microorganisms are identified and found to be sensitive to less toxic antibacterial agents. Prolonged release of the antibiotic from the adrenal cortex may produce effective post antibiotic effect for a long period following discontinuation of the antibiotic. ° **Pneumonia**: An aminoglycoside in combination with a β-lactam antibiotic is indicated for empirical therapy of hospital acquired pneumonia in which multi drug resistant, gram-negative aerobes or *Pseudomonas* may most likely be causative pathogens. Therapy with aminoglycoside alone not recommended because of difficulties in achieving therapeutic concentrations owing to relatively poor penetration of the drug into inflamed tissues. Also, low oxygen tension and low pH are associated with pneumonia and both these condition are known to interfere with aminoglycoside activity. The agents are not to be used in treating community acquired pneumonia in which *Streptococcus pneumoniae* and *anaerobes* are most likely implicating pathogens.	filtration rate with gradual rise in serum creatinine after a few days of therapy. – Encountered more with longer courses of aminoglycoside therapy (Chambers, 2001:1229). – Reduction in glomerular filtration rate believed to be due to activation of the renin-angiotensin system (RAS) (Mingeot-Leclercq & Tulkens, 1999:1005). Biochemical events leading to the activation of RAS are attributable to the cationic nature of the aminoglycosides. This property of the drug molecules according to Chambers (2001:1229) enables them to interact with anionic phospholipids and impair the generation of membrane derived autacoids and intracellular second messengers such as prostaglandins, inositol triphosphate and diacylglycerol. The drugs also inhibit various phospholipases, sphingomyelinases, ATPases and alter the functions of mitochondria to result in perturbations of the structure of cellular membranes. The net result of these is constriction of renal vasculature and a reduction in renal blood flow which in turn stimulates the RAS.

Antibiotic	Spectra of activity and Therapeutic applications	Associated side effects and drug interactions
	° **Meningitis**: Aminoglycosides may be used in treating meningitis only if implicating pathogens are gram-negative bacteria resistant to β-lactam antibiotics. Direct administration of the drugs into the cerebral ventricles in such cases would be required. ° **Gram-positive infections**: Penicillin plus gentamicin is indicated for enterococcal endocarditis. Staphylococcal tricuspid valve endocarditis in injection drug users may also be treated with gentamicin or tobramycin in combination with nafcillin. ° **Sepsis**: *P. aeruginosa* is a suspect as causative pathogen in granulocytopenic patients with sepsis. The newer aminoglycosides given in combination with an antipseudomonal penicillin is recommended in treating such infections. Aminoglycosides, as noted by Sabella and Goldfarb (1999:9), continue to be used for empiric therapy in neonatal sepsis in absence of proofs of improved treatment outcomes supposedly associated with the more frequent use of the 3rd generation cephalosporins in treating gram-negative meningitis in this patient group. • **Notations on individual aminoglycosides:** – Amikacin is resistant to many of the common plasmid mediated enzymes. Many strains resistant to gentamicin and tobramycin will be susceptible to amikacin for this reason (Sabella & Goldfarb, 1999:9).	– Non-steroidal anti-inflammatory agents aggravate aminoglycoside nephrotoxicity because of their inhibition of vasodilatory prostaglandin PGE2 production (Mingeot-Leclercq & Tulkens, 1999:1005). ° **Other aminoglycoside associated toxicities** – Acute neuromuscular blockade and apnoea has been reported with the use of the aminoglycosides. May result in severe respiratory depression. The order of decreasing potency for blockade is neomycin □ kanamycin □ amikacin □ gentamicin □ tobramycin (Chambers, 2001:1230; Archer & Polk2005:802). ° **Aminoglycoside incompatibilities/interactions** – Aminoglycosides can be inactivated by various penicillins in vitro and in patients with end stage renal failure. They are never to be mixed in the same bottle with the penicillin. Other drugs with which they show similar incompatibilities include the cephalosporins, heparin, and amphotericin B (Chambers, 2001:1232).

Antibiotic	Spectra of activity and Therapeutic applications	Associated side effects and drug interactions
Quinolones/ Fluoroquinolones – Nalidixic acid – Ciprofloxacin – Norfloxacin – Ofloxacin – Enoxacin` **Advanced generation fluoroquinolones** – Gatifloxacin – Levofloxacin – Moxifloxacin – Sparfloxacin	• **Spectra of activity** Potent bactericidal agents against *E. coli*, *Salmonella*, *Shigella*, *Enterobacter*, *Campylobacter* and *Neisseria* (Chambers, 2001:1181) Ampicillin resistant strains of E. coli are almost uniformly resistant to the new quinolones (Blondeau, 1999:14). All fluoroquinolones are active against Enterobacteriaceae and *H influenzae,* however and in contrast to gram-positive bacteria, the newer fluoroquinolones are inferior to ciprofloxacin in their activity against gram-negative bacteria. Also the newer fluoroquinolones (gatifloxacin, levofloxacin, moxifloxacin) are more active against atypical pathogens , namely, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* in comparison with the older fluoroquinolones (ciprofloxacin and norfloxacin) (Cross Jr., 2001:214). The newer fluoroquinolones (grepafloxacin, gatifloxacin, clinafloxacin, moxifloxacin) are distinguished by their enhanced antimicrobial activity against clinically important gram-positive organisms e.g. *Streptococcus pneumoniae, Enterococcus* spp, *StreptococcuS. pyogenes, Staphylococcus aureus* (Chambers, 2001:1181; Blondeau, 1999:10). Greatest activity against gram-positive pathogens is demonstrated by moxifloxacin and clinafloxacin. Trovafloxacin among the newer agents have remarkable activity against anaerobic bacteria and is indicated for abdominal anaerobic infections. Anaerobes generally are less susceptible to the fluoroquinolones (Cross Jr., 2001:214).	• **Adverse effects** Side effects or adverse effects associated with fluoroquinolones as reported by Bertino and Fish, (2000:802, 803) include the following: – Gastrointestinal upsets including nausea, vomiting diarrhoea, constipation and abdominal pain. – Central nervous system reactions demonstrating as headache and dizziness. – Skin reactions (rash and pruritus) Adverse effects often but less commonly reported include convulsions, psychosis, tendonitis, hypersensitivity and photosensitivity reactions and prolongation of QT interval on the electrocardiogram particularly with the newer agents sparfloxacin and grepafloxacin, though not with levofloxacin (Blondeau, 1999: 24; Cross jr., 2001:217). • **Drug interactions** Documented drug interactions with the fluoroquinolones include: – Reduction in bioavailability when given with compounds containing multivalent metal ions. All fluoroquinolones interact with compounds containing multivalent metals

Antibiotic	Spectra of activity and Therapeutic applications	Associated side effects and drug interactions
	• **Therapeutic applications** Different generation classifications of fluoroquinolones are generally indicated for the following infections: – 1st generation (Nalidixic acid and Cinoxacin): Used in uncomplicated urinary tract infection UTIs – 2nd generation (lomefloxacin, norfloxacin, enoxacin, ofloxacin and ciprofloxacin): Used in uncomplicated and complicated UTIs, pyelonephritis, sexually transmitted infections, prostatitis, skin and soft tissue infections – 3rd generation (Sparfloxacin, gatifloxacin, levofloxacin, Moxifloxacin) Used in acute exacerbations of chronic bronchitis, sinusitis, community acquired pneumonia – 4th generation (Trovafloxacin) Used for same infections as the 3rd generation drugs plus intraabdominal infections, nosocomial pneumonia and pelvic infections. Not indicated for complicated UTI and pyelonephritis (Jones & Mandell, 2002:70), Fluoroquinolones are currently used to treat resistant cases of Mycobacterium tuberculosis infection but are also under study for first line use in the treatment of these infections (Ginsburg *et al.*, 3003:432)	including calcium, iron, aluminium or zinc. Concomitant administration with drug preparations containing these metals can result in significant reductions in bioavailability of the agents (Cross Jr., 2001:217). – Increase in theophylline plasma concentration when the two drugs are used concurrently. Fluoroquinolones with modifications at C-1, C-7 and C-8 (enoxacin, ciprofloxacin) can interact with theophylline and caffeine. The agents also inhibit cytochrome P-450 (Schaeffer,2003:134) and may cause an increase in theophylline plasma levels (Chambers, 2001: 1182.). – Reports of induction of seizures when used concomitantly with fenbufen. Non steroidal anti inflammatory agents potentiate central nervous system effects of the fluoroquinolones by augmenting the displacement of γ-amino butyric acid (GABA) from its binding sites in the brain. Seizures were reported with the concomitant use enoxacin with fenbufen (Chambers, 2001:1182).

Antibiotic	Spectra of activity and Therapeutic applications	Associated side effects and drug interactions
Sulfamethoxazole-Trimethoprim (Co-trimoxazole)	• **Spectrum of activity** Antibacterial spectrum covers a large number of gram-positive and gram-negative bacteria. Chambers (2001:1177) made notations on resistance patterns of most common pathogens to the antibacterial agent as follows: – *Chlamydia diphtheriae* and *Neisseria meningitidis* susceptible to co-trimoxazole. – Most *Streptococcus pneumoniae* sensitive to co-trimoxazole but with high rates of resistance development. – From 50% to 95% of strains *Staphylococcus aureus, Streptococcus pyogenes*, the viridans group of streptococci, *Escherichia coli*, *Klebsiella* spp, *Proteus mirabilis*, *P. morganii*, *P. rettgerri*, *Enterobacter* spp, *Brucella abortus*, *Yersinia* spp and *Norcardia asteroides* are sensitive to co-trimoxazole. – Rapid emergence of bacterial resistance to co-trimoxazole with the emergence of resistant *S. aureus* and *Enterobacteriaceae* particularly being considered a special problem among AIDS patients receiving the drug for prophylaxis of *Pneumocystis carinii* pneumonia (Martin *et al.*, 1999:1809) • **Therapeutic applications** Co-trimoxazole is useful in treating the following according to Chambers (2001: 1178) and Archer and Polk 2005:800). ° **Urinary tract infection** – Uncomplicated urinary tract infections (UTIs) – Recurrent UTI in women and prostatitis in men	• **Adverse effects** Only little toxicity associated with co-trimoxazole in routine use. Important among these include, as documented from Chambers (2001:1178) and Archer and Polk, 2005:802, ° Dermatologic adverse reactions. Most common of all adverse reactions seen with the antibacterial agent. HIV patient mainly demonstrate these side effects which in most patients may show as – minor skin rashes including maculopapular rashes and urticarial reactions appearing after one week of therapy. – more serious dermatological reactions like exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrosis. ° Trimethoprim interferes with renal secretion of potassium and co-trimoxazole may cause hyperkalaemia particularly in HIV patients on high doses of the agent for PCP. ° Gastrointestinal side effects including nausea and vomiting and also glossitis and stomatitis ° Mild and transient jaundice, probably a demonstration of allergic cholestatic

Antibiotic	Spectra of activity and Therapeutic applications	Associated side effects and drug interactions
	° **Respiratory tract infections** – Acute exacerbations of chronic obstructive airways disease. – Not recommended in treating streptococcal pharyngitis since it does not eradicate the pathogens. ° **Gastrointestinal tract infections** – Alternative to fluoroquinolones in treating shigellosis. – Second line drug to ceftriaxone or a fluoroquinolone for typhoid fever. – Acute diarrhoea caused by enteropathogenic *E. coli.* May increase risk of haemolytic uraemic syndrome, possibly by increasing shiga toxin release by bacteria (Wong, 2000:1930). ° ***Pneumocystis carinii* pneumonia (PCP)** High dose therapy (trimethoprim, 20 mg/kg/day and sulfamethoxazole 100 mg/kg/day effective for severe infection in AIDS patients. Lower dose therapy (800 mg sulfamethoxazole and 160 mg trimethoprim) given daily can be used in patients with less severe PCP. Same dose given once daily or twice daily can be used in preventing PCP in the patient group.	jaundice. Abusin & Johnson (2008:1) documented a case study in which co-trimoxazole was seen to induce hepatotoxicity. ° Central nervous system (CNS) reactions may be experienced as headache, depression and hallucinations. ° The agents may also cause haematological complications demonstrating as various blood disorders including coagulation disorders, agranulocytosis, granulocytopenia, purpura and sulfhaemoglobinaemia and various types of anaemia (including aplastic , haemolytic and macrocytic) ° Permanent impairment of renal function may follow the use of co-trimoxazole in patients with renal disease.
Metronidazole	• **Spectrum of activity** Spectrum of metronidazole is limited to obligate anaerobic bacteria especially gram-negative species e.g. *Bacteroides* and *Fusobacterium*, *Helicobacter* spp and spore forming gram-positive bacilli e.g. *Clostridium* spp. It is less active against anaerobic gram-positive cocci e.g. *Peptococcus* and *Peptostreptococcus* and) (Chambers, 2001:1107; Land & Johnson, 1999:290).	• **Adverse effects** Serious adverse reactions to metronidazole are uncommon. Most common among these according to Chambers (2001:1107) and Archer and Polk (2005:802) include: ° Headache, nausea, dry mouth and metallic taste

Antibiotic	Spectra of activity and Therapeutic applications	Associated side effects and drug interactions
	• **Therapeutic applications** Because of its spectrum and its ability to penetrate into the area of infection, metronidazole is one of the drugs of choice for treatment of any abscess in which the involvement of obligate anaerobes is suspected (e.g. lung, brain, or intraabdominal abscesses. It also the drug of choice in treating bacterial vaginosis and antibiotic associated pseudomembranous colitis (Archer & Polk, 2005:800).	° Vomiting, diarrhoea, and abdominal distress may be experienced. ° Furry tongue, glossitis and stomatitis occurring during therapy may be due to exacerbating moniliasis. ° CNS effects including dizziness, vertigo, and very rarely encephalopathy, convulsions, incoordination and ataxia may occur and warrant discontinuation of the drug. Drug should be withdrawn if numbness and / or paresthesias of the extremities occur. ° Urticaria, flushing and pruritus are indicative of drug sensitivity that requires withdrawal of the drug. ° Dysuria, cystitis, and a sense of pelvic pressure have been reported. ° Disulfiram like effects following ingestion of alcoholic beverages within 3 days of drug therapy are documented with metronidazole use. Patients may experience abdominal discomfort, vomiting, flushing or headache. ° Metronidazole in high doses and given for long periods showed carcinogenic and mutagenic effects in rodents. The drug is to be avoided in pregnancy, particularly within the first trimester for these concerns. There

Antibiotic	Spectra of activity and Therapeutic applications	Associated side effects and drug interactions
		is no evidence however that metronidazole given in therapeutic doses poses any significant risk of cancer to human patients. • **Drug interactions** Drug interactions documented with the use of metronidazole include the following: – Precipitations of CNS signs of lithium toxicity in patient on high doses of lithium – Prolongation of prothrombin time of patients receiving coumadin anticoagulants – Elevation of metronidazole plasma levels when taken concomitantly with inhibitors of cytochrome P450 e.g. cimetidine.

2.5 Appropriate antibiotic prescribing: Definition and principles

Antibiotics are generally prescribed for empirical and definitive treatment and also in the prophylaxis or prevention of infections (Chambers, 2001:1146). Prescribed for either of these purposes, the primary objective is always to achieve selective activity of the antibiotic against infecting or potentially infecting pathogens, without causing toxicity or allergic reactions in the patient.

Unlike most drugs whose basic mechanisms of action involve their direct modulation of the body's physiological processes, the therapeutic effects of antibiotics are directed at elimination or inhibition of bacterial pathogens implicated in infections. Their efficacies generally depend on their abilities to eradicate or inhibit growth of such pathogens at certain minimum achievable plasma concentrations when their indicated doses and dosage regimens are administered. Any direct effect they may have on the body's physiological processes may show as manifestations of their adverse effects. By implication and to be considered prescribed appropriately or rationally, antibiotics should in principle be selected to target infecting pathogens and prescribed in dosage regimens only necessary to provide minimum drug concentrations required for bacterial growth inhibition without exposing recipient patient to avoidable adverse drug effects. In a review on antibiotic prescribing, Klugman (2003:S27) defined appropriate prescribing of antibiotics as "maximising the potential of clinical cure by maximising the potential for bacterial eradication". In order to achieve this he pointed out that first and foremost, antimicrobials should be used only to treat bacterial infections. This, according to him, is not often stressed enough (or at all) in published guidelines, reflecting as he further stated, difficulties in diagnosing bacterial infections in clinical practice. Expressing a similar concern, Chambers (2001:1143) noted that it is commonplace for decisions to prescribe antibiotics to be made lightly without regard to the infecting microorganisms or the pharmacological features of the drug. Prescribed this way, the use of an antibiotic can be considered as being irrational or inappropriate. Apart from having the disadvantage of orchestrating the stage for the emergence of resistant strains of otherwise susceptible pathogens, inappropriate prescribing and use of antibiotics serve as a significant contributing factor in failures encountered in the treatment of infections (Towsend & Ridgway, 2005:293; Niederman, 2005:S172).

For an appropriate antimicrobial therapy that ensures maximum therapeutic benefits to the patient, it is critical that antibiotics are selected based on principles that take into consideration the nature of the infection, the pharmacological properties of prescribed antimicrobial agents and the clinical profile of the patient (Chambers, 2001:1146; Guglielmo, 2008: 56-1, 56-7). In principle, and as Finch (2005:42) indicated, it is important to make initial clinical assessment of the patient to establish the presence of infection before deciding to use the antimicrobial agent. Such an assessment should ideally be supported by laboratory investigations to establish definitive microbial diagnosis (Finch (2005:42). Other authors stated, as required principles to be followed in appropriate antibiotic prescribing for as prescriber to have knowledge of most likely pathogens involved in an infection as well as their antibiotic sensitivity patterns before attempting empiric antibiotic treatment. Towsend and Ridgeway (2005:294) in this regard noted "having identified a likely focus of infection, an appropriate empirical regimen relies on knowledge of the range of organisms likely to be implicated in the infection and also on local susceptibility patterns". Sabella and Goldfarb (1999:3) also similarly stated that, "because antimicrobial therapy most often is initiated empirically, identifying the site of infection and having a thorough knowledge of the likely pathogens causing infections at that site are critical". According to the authors, it is equally important to know the susceptibility patterns of the pathogens, preferably based on contemporary local community and hospital data". By these statements, the authors meant to underscore the importance of prescribers' identification of a site of infection and their having knowledge of pathogens associated with infections at such a site (their local antibiotic sensitivity patterns inclusive) in order to be in the position to prescribe antibiotics appropriately in the treatment of infections.

In few infectious diseases clinical assessment can confidently predict a specific microbial aetiology (Finch, 2005:42). The author gave the following examples to illustrate his point:

- Erysipelas, which are caused primarily by *StreptococcuS. pyogenes.*
- Impetigo, which may be caused by either *S. pyogenes* or *Staphylococcus aureus* or both.
- Clinical manifestations of herpes simplex infection which usually are diagnostic of this infection.
- Community acquired pneumonia which most of the time is caused by *S. pneumoniae*, though other organisms like *Staphylococcus aureus* may need to be considered.

- Meningitis in infancy which usually is an infection of *Neisseria meningitidis* or *S. pneumoniae or Haemophilus influenzae*.
- Meningitis in neonates for which *Escherichia coli* and group B streptococci are known predominant pathogens.
- Dysuria and frequency accompanied by loin pain indicating pyelonephritis which often is caused by gram-negative enteric pathogens.

For hospitalised and severely ill patients it is important in principle, to establish microbial cause of an infection (Finch, 2005:43). The clinician may find the need to initiate antibiotic therapy based on presumptive bacteriological diagnosis in such circumstances. It is required in situations of that sort for appropriate specimens of the presumed site of infection to be taken for culturing and sensitivity testing prior to the institution of antibiotic therapy (Finch, 2005:43; Chambers, 2001:1159).

Clinical assessment of the patient to establish an infection as Finch (2005:42) indicated involves prescribers' physical examination of the patient, taking notes of presenting signs and symptoms and requesting, where necessary, for laboratory investigations in a diagnostic workup aimed at establishing the presence of bacterial infection before antibiotics are prescribed. Signs and symptoms of infection that are of value in establishing presence of infection may include fever, elevated white blood count (symptoms of inflammatory responses to infections), low blood pressure as seen in septicaemia, pus production in superficial infections and purulent sputum, decreased breath sounds, rhonchi or abnormal chest x-ray findings which may be present in pulmonary infections (Guglielmo 2008: 56-4, 56-5, 56-6; Towsend & Ridgeway 2005:294). Presence of fever needs further evaluation before diagnostic conclusions of bacterial infections are made. Other clinical conditions, for example viral infections and neoplastic autoimmune disorders, which are not indicative of bacterial infections, may be the cause of the fever (Guglielmo 2008: 56-4). Most physicians by reflex action associate fever with bacterial infections and erroneously prescribe antibiotics without further evaluation. This practice is irrational and potentially dangerous according to Chambers (2001:1146).

Establishing the precise site of an infection as indicated by Guglielmo (2008::56:5), allows for obtaining specimens, where possible, for an initial microscopic investigation to

determine morphological characteristics of infecting pathogens. At some given body sites, it also enables associations of certain categories or even specific pathogens with infections further to the author's indications. Such associations as Guglielmo (2008:56:6) cautioned, however, must be done in the consideration that pathogens which would under normal circumstances be associated with infections at such sites, can be altered by concomitant disease states or factors contributing to the contraction of the infection. According to the author, pneumonia acquired in the community, for example, is associated with *S. pneumoniae*, viruses and mycoplasmas in normal hosts. In patients with chronic obstructive airways disease, pathogens implicated with the infection are most likely to be *S. pneumoniae*, *Haemophillus influenzae*, *Legionella*, *Chlamydia* and *Mycoplasma*. In aspiration pneumonia in either category of patient groups, the microbial flora normally associated with the infection would be altered by the presence of normal aerobic or anaerobic mouth flora. Gram-negative aerobic bacteria would be less likely associated pathogens as they would be in aspiration bacteria acquired in the hospital.

Knowing the site of an infection as a required principle in antibiotic prescribing is also necessary in some instances for purposes of making appropriate choices of antibiotics. The ability of antibiotics to distribute and concentrate at sites of infection sometimes, become the deciding factor in selecting antibiotics or prescribing them at given doses in treating infections at certain anatomic body sites. Thompson and Wright (1998:998) highlighted this point in their presentation on general principles of antibiotic prescribing. They stated that to be effective, an antibacterial agent must reach the site of infection in adequate concentration and must resist inactivation by physical or microbial factors. By this statement, the authors meant to re-echo the necessity of identifying the sites of an infection and knowing the extent of availability of administered antibiotics at such sites before taking decisions on which antibiotics to prescribe in treating such infections. They gave the following examples to illustrate their point:

- Infections at sites such as the ocular orbit, the CNS, cerebrospinal fluid, biliary tract, abscess cavity and bone may require higher serum levels for penetration.
- Some drugs do not cross the blood brain barrier and are not suitable in treating infections at such sites.
- Some drugs do not penetrate respiratory secretions and are less desirable for the treatment of pneumonia.

- Most drugs poorly penetrate the prostate gland and those that do penetrate are often not active against the pathogens that cause prostatitis.
- Most drugs are not efficacious in the acidic, low-redox potential environment of abscess fluid.

Antibiotics can be prescribed in the prophylaxis or suppression of infections (Thompson & Wright, 1998:997). To justify the prescribing of the agents in such circumstances, however, potential sources of infections or factors that may predispose the patient to infection should be present. Examples of such sources include intubations and presence at certain anatomic sites of patients, of prosthetic valves, catheters, intravenous lines (Guglielmo, 2008::56:5), or the presence of co-morbid conditions and wounds or cuts as may be inflicted through surgical procedures or injuries. Literature documentations outlined below substantiate these as proven sources of infections that may warrant prophylactic or suppressive antibiotic treatment for as long as they are known to be present in the patient. They include,

- The use of percutaneous vascular closure devices (PVCDs) in haemostasis of arteriotomy sites were found to be complicated with access-site infections in a study in which Sohail *et al.* (2005:1012) investigated infectious complications of PVCDs.
- Darouiche's (2001:1567) documentation that medical devices are responsible for a large portion of nosocomial infections. The pathogenesis of device associated infection according to the author, centres around a multifaceted interaction among the bacteria, the device and the host.
- Indication of Fariňas *et al.* (2006:1284) that prosthetic valve endocarditis (PVE) is a serious complication of cardiac valve replacement. In a study in which the researchers investigated risk factors associated with contraction of the infection, they established that patients who have had an episode of endocarditis before valve replacement surgery have fourfold to six-fold chances of developing the infection.
- Intravascular catheter-related infections being established as major causes of morbidity and mortality in the United States, with coagulase-negative staphylococci, *Staphylococcus aureus*, aerobic gram-negative bacilli and *Candida albicans* being recognised as the most commonly cause of such infections (Mermel *et al.*, 2001:1249).
- Indications by Jeelani *et al.* (2009:166,167) that infection are the most significant early complication of cerebrospinal fluid (CSF) shunt placement and also notations

of the presence of a CSF leak at the surgical site as the biggest risk factor for such infections.

- Demonstration of co-trimoxazole prophylaxis of opportunistic infections in HIV (human immunodeficiency virus) patients with tuberculosis in the reduction of mortality rates in these patient groups (*Grimwade et al.*, 2005:166).

In principled antibiotic prescribing, knowledge of potential sources of infections in the patient is seen to provide means of predicting the potential target pathogens to enable the appropriate choices of antibiotics and decisions on durations of such treatments, to be made. Elaborating on prophylactic use of antibiotics (Thompson & Wright, 1998:997) gave the examples of penicillin and co-trimoxazole being used respectively as single antibiotics and for long durations of treatment in preventing rheumatic fever and *Pneumocystis carinii* pneumonia. The use of these agents in ways described according to the authors is allowed because these infections are caused by specific organisms that are regularly sensitive to the agents used. According to the authors' further indications, when prophylaxis is directed against multiple possible pathogens such as in surgical wound prophylaxis, it is effective only in a short term. Also, where known potential sources of infections give rise to infections that cannot be cured as may be seen in the cases of prosthetic valves, antibiotics can be prescribed to suppress such infections for variable long periods.

The prescribing of antibiotics in combination may be necessary in polymicrobial infections. The guiding principle in such circumstances takes into consideration the combined clinical effectiveness of the prescribed antibiotics. The drugs could be given for purposes of synergy to achieve bactericidal activity against infecting microorganisms or prevent resistance from developing. They may also be given in the empiric therapy of possibly resistant gram-negative infections in the immunocompromised patient (Sabella & Goldfarb, 1999:3; Thompson & Wright: 1998:997). The combination of a penicillin and an aminoglycoside has been shown to be synergistic for the treatment of enterococcal endocarditis and neonatal group B streptococcal sepsis. It is also used frequently to provide synergy and to prevent the emergence of antimicrobial resistance in the treatment of serious infections *Pseudomonas aeruginosa* and *Klebsiella pneumonia* in the immunocompromised host (Sabella & Goldfarb, 1999:3; Finch, 2005:46). Concurrent use of certain antibiotics may have antagonistic effects with reduced

efficacies of either antibiotic. This is exemplified by documented antagonistic effects of the concurrent use of tetracycline (bacteriostatic antibiotic) and penicillin (a bactericidal antibiotic) (Finch, 2005:46) or of the macrolides, clindamycin and chloramphenicol (Chambers, 2001:1247). Some other antibiotics may show no difference in their activities when used concurrently. When they display no difference in their activities, the effect of the combined use of two antibiotics will be seen not to be better than the effect of the more active of the two agents used alone (Archer & Polk 2005:797; Guglielmo, 2008::56:23). Concurrent prescribing of antibiotics with antagonistic effects should in principle be avoided on accounts of their lack of any therapeutic advantages they may be expected to have over the singly prescribed agents.

Before the initial therapy of community acquired pneumonia is commenced in seriously ill or hospitalised patients, Bartlett *et al.* (2000:347) stipulated in guidelines developed by Infectious Diseases Society of America (IDSA) that Gram stain and culture of sputum should be carried out in inpatients with the infection. According to the authors this is optional for outpatients. While establishing Gram stain and morphological characteristics of infecting pathogens enables essentially more rational selection of initial and empiric antibiotic therapy, in the critically ill patient, culture sensitivity tests provides means of definitive antibiotic treatment in the patient group (Thompson & Wright, 1998 :997).

On the basis of the above reviewed principles in antibiotic prescribing, the following are formulated as principles which prescribers need to observe to be seen as appropriately prescribing antibiotics based on antibiotic need establishment as well as the selection of antibiotics deemed appropriate in treating diagnosed infections. These have been used as reference points in developing criteria used in assessing the appropriateness of antibiotic prescriptions as studied in this research. These include:

- **Establishing presence of bacterial infections prior to antibiotic prescribing.**
  Presence of bacterial infections can be established in principle prior to antibiotic prescribing through appropriate clinical assessment of patients in which,
  - signs and symptoms of infection should be precisely identified;
  - meticulous physical examination of patients carried out for precise diagnosis of infection;

- laboratory investigations must be carried out, where possible, to support clinical findings on physical examination; and
- sites of infections clearly established to enable appropriate targeting of infecting pathogens and the appropriate selection of antibiotics for their treatment.

- **Establishing potential sources of infections or co-morbid conditions predisposing patients to certain infections prior to antibiotic prescribing for prophylaxis.**

  This is considered a pre-requisite for:
  - appropriate prediction of would be infecting pathogens in infection prophylaxis.
  - deciding on appropriate antibiotics and their regimens to be employed in infection prophylaxis

- **Taking specimens and requesting for culture sensitivity tests (CST) prior to empiric antibiotic treatment initiation in critically ill or hospitalised patients.**

  Definitive antimicrobial therapy programmes based on precise identification of infecting pathogens are required in critically ill or hospitalised patients.
  - Morphological identification of pathogens through rapid Gram's staining of specimens should be done in these circumstances where possible to enable more appropriate choices of antibiotics to be made in initial empiric antibiotic treatment.
  - With results of CSTs known, initial antibiotic therapies should be revised in favour of agents that are active against infecting pathogens and also have the most favourable pharmacological and pharmacokinetic profiles among the group of agents from which antibiotic selections are to be made for the definitive treatment.

- **Making appropriate antibiotic selections for empiric or definitive treatment of infections.**

  This in principle must be based on the following:
  - local bacterial pathogen sensitivity patterns;
  - pharmacokinetic profiles of antibiotics with respect to distributions into and concentration at sites of infection; and
  - the compatibility and extent of combined effectiveness of antibiotics when prescribed concurrently in the event of multiple antibiotic therapies. Considerations in this respect should be given to synergistic or antagonistic effects in activities of the prescribed antibiotics.

2.6 Assessing appropriateness of antibiotic prescriptions: Merits and demerits of methods

Presenting editors' view on the British Journal of Clinical Pharmacology, Aronson (2004:229) stated that "appropriate prescribing" depends on an understanding of the pathophysiology of a clinical problem and the pharmacology of drugs available to treat it. While other drugs are prescribed to treat illnesses on the basis of their abilities to directly modulate physiological processes and counteract disease processes, antimicrobial agents are prescribed in the treatment of illnesses on accounts of their abilities to indirectly terminate disease processes through the elimination of the aetiological agents - the microbial pathogens - of such illnesses. Any direct pharmacological effects they may have on the body's systems may manifest as their unwanted, rather than being desired effects. The appropriate prescribing of antibiotics viewed from this perspective can be seen as depending not only on an understanding of the pathophysiology of the problem or the pharmacological effects of prescribed antimicrobial agents, but also on understanding the pathogenic characteristics of bacteria implicated in an infectious disease and the disposition of such bacteria to antimicrobial killing.

Making clinical decisions to initiate antibiotic therapy can be challenging as this calls for the establishment of the presence of an infection to justify the decision to prescribe an antibiotic. In some category of patients as in the cases of persons in long-term-care facilities cited as an example by Loeb *et al.* (2001:120), it can be difficult to establish a diagnosis of infection. In some other cases, diagnosis of bacterial infections may be made difficult because of the resemblance of clinical symptoms classically identified with certain bacterial infections with symptoms of certain other types of disease conditions that do not have pathogenic bacteria as an underlying cause. Classical examples are the similarities of symptoms of viral and bacterial infections of the respiratory tract (Gonzales *et al.*, 2001:491,493), protozoal infections (e.g. vaginal trichomoniasis) of the vagina manifesting as discharges with similar descriptions of those seen with bacterial infections (e.g. genitourinary tract infections caused by *Neisseria gonorrhoea* or *Chlamydia trachomatis*) (Holmes, 2005:765). Even in cases where bacteria pathogens may be aetiologies of diagnosed infections, a prescribed antibiotic for such an infection may be considered inappropriate if it does not target the exact pathogen causing the infection (Aronson, 2004:229). By implication, this means that even if an infection is diagnosed as being of bacterial aetiology, an antibiotic can be considered appropriately

prescribed only when it is active against the infecting pathogens. With such considerations, the assessment of the appropriateness of antibiotic prescriptions can be envisaged to be difficult and complicated.

According to what the objectives of their studies entail, researchers are seen to use different methods in assessing the appropriateness of antibiotic prescriptions as a search of the literature has shown. Examples of these methods as employed by a number of researchers in studies involving assessment of antibiotic prescriptions are cited as follows:

- Thuong *et al.* (2000: 501,502) studied the appropriate use of restricted antimicrobial agents in Henri Mondor hospital in France. In assessing the appropriateness of antibiotic prescriptions in this study, the researchers used procedures that involved the evaluation of prescriptions against a set of criteria formulated by senior physicians with expertise in infectious diseases from information provided in standard treatment guidelines developed for the use of such restricted antibiotics.
- Erbay *et al.* (2009:53), studying patterns of antibiotic use in intensive care units of a tertiary care hospital in Turkey, evaluated the appropriateness of antibiotic prescriptions in relation to diagnosis and bacteriological findings. They used procedures in which the appropriateness of antibiotic prescriptions were determined based on judgements of two infectious disease experts who examined antibiotic prescriptions and took decisions on their appropriateness.
- Martinez *et al.* (2007:235) assessed the appropriateness of antibiotic prescriptions given for the treatment of urinary tract infections in adults in several hospital emergencies in Spain. They used assessment methodologies based on conformities of assessed prescriptions to criteria of appropriateness established by a panel of experts at a consensus conference. The prescriptions by this method were classified into first choice, second choice and inappropriate prescriptions for treating the infections.
- Loeb *et al.* (2001:376), assessed appropriateness of the initiation of empiric antibiotic therapy in residents of long-term care facilities by investigating cases in which these agents are prescribed only when clinical criteria for infection were met. In their methodology, they used standardised consensus definitions of infection for long-term care facilities and determined how often clinical criteria for infections were met before antibiotics were prescribed.

- Trap and Hansen, (2002:883), in a study carried out in Harare, designed and used a method that measured the appropriateness of co-trimoxazole prescribing based on a prescription "correctness score list" developed by a panel of evaluators. The panel assessed these prescriptions as written by dispensing and non dispensing doctors and based their evaluations on both the diagnoses and symptoms for which they were prescribed and the conformities of these to recommendations in the national standard treatment guidelines.
- Alves da Cunha *et al.* (2003:8), studying extents of inappropriate prescribing of antibiotics for children with acute respiratory infection (ARI) in Brazil, assessed appropriateness of prescribed antibiotics by evaluating antibiotic prescriptions given for the treatment of the infection in children against recommended management proposed in the national guidelines. Assessment by a paediatrician trained in the ARI Brazilian guidelines was taken as the gold standard. The researchers notably did not include the choice of antibiotic and dose used in the criteria for determining appropriateness of therapy.
- Maciulaitis *et al.* (2006:999) investigated the extent to which antibiotics are appropriately prescribed in a retrospective study in which antibiotic prescription records were assessed. In this study the researchers evaluated the appropriateness of antibiotic therapy according to prescribers' adherence to published guidelines.
- Akkerman *et al.* (2005:570) in a study determined the extent of under- and over-prescribing of antibiotics in acute otitis media (AOM) in general practice in the Netherlands. For their method of assessment in this study, they converted recommendations of the national guideline on AOM of the Dutch College of General Practitioners into criteria by three general practitioners with expertise in AOM. The criteria were put into an algorithm and used in an analytical procedure which enabled the categorisation of all AOM consultations according to antibiotic indication and prescribing. The categories included:
  - antibiotic indicated and prescribed (category A),
  - antibiotics not indicated but prescribed (over-prescribing) (category B),
  - antibiotics indicated but not prescribed (under-prescribing) (category C) and
  - antibiotics not indicated and not prescribed (category C).

Writing on the subject matter of developing a measure for the appropriateness of prescribing, Britten *et al.* (2003:246) acknowledged the development by researchers of

various instruments for measuring appropriateness of prescriptions. They mentioned two such measures, the medication appropriateness index (MAI) and prescribing appropriateness index (PAI) which were developed by different researchers and used in measuring appropriateness of prescribing in general practice. MAI was based on a review of the literature and consisted of 10 questions which were asked of any prescription recorded in a patient's case notes. The questions covered issues such as indication of the drug, efficacy and interactions. PAI was based on a review of the literature like MAI, and also on opinions of an expert panel and consisted of 9 indicators which were used in judging prescribing by general practitioners.

The objectives for which antibiotic prescriptions are assessed for their appropriateness are varied and are most logically determinants of the types of instruments researchers develop for such assessments. In a way also, variations in the instruments researchers use in determining the appropriateness of antibiotic prescriptions could be deemed reflective of what researchers consider important in assigning appropriateness to such prescriptions. Reservations expressed by Aronson (2004:230) regarding numerical weightings given to the 10 questions used in MAI for assessing the appropriateness of drug prescribing in general practice, explain this. MAI was designed for measuring appropriateness of drug prescribing generally and hence can be used to assess appropriateness of antibiotic prescriptions. The first two questions in the index which were meant to investigate whether a prescribed drug was indicated for the condition for which it is prescribed and whether it is effective in treating the condition, were each given a numerical weighting of 3 (three). The next four questions which respectively investigate the correctness of dose of prescribed drug, directions for its use, practicality of directions given for its use and its interactions with other drugs prescribed with it, were given a weighting of 2 (two) each. The last four questions which dealt with drug-disease interactions, unnecessary duplications of prescribed drugs, acceptability of duration of therapy and cost of drug were also each given weightings of 1 (one). In Aronson's (2004:230) opinion, the second question which investigated the effectiveness of prescribed drug was not given sufficient weighting. In support of his opinion, he argued that if the drug is ineffective then the prescription is inappropriate and none of the other questions matters. It follows logically then that if the editor (Aronson) were to use the MAI as an instrument in assessing a sample of prescriptions he would modify it to reflect what is most important in his opinion to measuring the appropriateness of prescriptions.

Further evidence substantiating speculations that variations in the instruments researchers use in determining the appropriateness of antibiotic prescriptions indeed might be reflective of what they consider as important in assigning appropriateness to prescriptions is provided by the following:

- comments by Trap and Hansen (2002:883) on methodologies employed by some researchers in assessing the appropriateness of antibiotic prescriptions and
- observed shortcomings of the instrument Trap and Hansen (2002:883) used in determining the appropriateness of co-trimoxazole prescribing.

The researchers commented that limitations some researchers placed on developing instruments for antibiotic prescription assessment in attempts to simplify their studies, result in "reduced value of such studies in depicting the real life situation". By this comment, the researchers in other words meant to state that antibiotic prescription assessment results of some studies become compromised by researchers not including some criteria in component questions of instruments they develop and use in assessing the appropriateness of antibiotic prescriptions. Such non-inclusion of a criterion in a research instrument for prescription assessment is deemed possible only when a researcher attaches less value to its importance as determinant of the appropriateness of an antibiotic prescription.

Trap and Hansen (2002:878-885) studied the appropriateness of co-trimoxazole prescribing by dispensing and non-dispensing doctors. To address what they considered as shortcomings of prescription assessment instruments used by researchers in studies they reviewed, they developed a method they described as "new". To them, this method "measured prescription rationality in a specific and realistic way". The instrument they used for measuring prescription appropriateness placed emphasis on the recorded diagnoses or symptoms for which the antibacterial agent was prescribed. In their opinion, assessing the appropriateness of prescriptions depends fully on recorded diagnoses or symptoms for which antibiotics are prescribed (Trap & Hansen, 2002:883). In their method of assessment, "correct" prescribing of co-trimoxazole was assumed if the antibacterial agent was prescribed for a diagnosis or symptom(s) included in a predetermined list of diagnoses or symptoms considered as infections or symptoms of infections. The instrument of measure of appropriateness of prescribing the antibacterial agent did not take into account records of any diagnostic workups confirming presence of bacterial infections. It obviously assumed that all diagnoses of infections provided in

the predetermined list have bacterial aetiologies. This is incorrect as some of the diagnoses or symptoms listed in the instrument, notably acute respiratory tract infection, upper respiratory tract infection and bronchitis, may have viral and not necessarily bacterial aetiologies (Gonzales *et al.*, 2001:491&493). Prescribing co-trimoxazole as an antibacterial agent for viral respiratory tract infections, though inappropriate, had been considered appropriate by the instrument employed by Trap and Hansen (2002:883) in assigning appropriateness to co-trimoxazole prescribing. In the opinion of the researchers, distinguishing between bacterial and non bacterial infections as clinical cases for which co-trimoxazole is prescribed is of less importance in determining the appropriateness of prescribing the antibacterial agent. Despite this observed shortcoming in their methodology, the researchers were able to achieve the objectives of their study which sought to establish differences in the appropriateness of co-trimoxazole prescribing by dispensing and non dispensing doctors.

An overview of prescription assessment methods reviewed above showed some common characteristics despite observed variations in instruments used in assessing prescriptions. These include basically:

- The development of instruments for data collation and analysis to determine the appropriateness of antibiotic prescriptions according to study objectives.
- Evaluations of assessed prescriptions against reference standards formulated from or combinations of any of the following,
  - standard treatment guidelines, [Trap and Hansen (2002:883), quoting a World Health Organisation reference, also indicated the common use of a list giving specific diagnoses or symptoms together with a list of products or therapeutic classes to be accepted as appropriate treatment.]
  - literature derived information or decisions of panels of experts on what should be considered appropriately or inappropriately prescribed antibiotics in given clinical scenarios.

On its face value, the use of prescribing guidelines as a standard reference in assessing antibiotic prescribing best evaluates the extent of prescribers' adherence to guidelines and prescribing policies enshrined in thereof, rather than the appropriateness of prescribed antibiotics *per se*. This is envisaged, particularly, if such guidelines do not include diagnostic algorithms for establishing absolute presence of diagnosed infections

to justify the prescribing of given antibiotics. Appropriate prescribing of antibiotics requires that an appropriate clinical assessment of the patients be carried out and antibiotic prescribing need clearly established prior to antibiotic prescribing (Finch, 2005:42). There are special cases for which antibiotic prescribing guidelines have been developed for infections that have been thoroughly studied (Thompson & Wright, (1998:1002). The authors gave examples of infective endocarditis, community acquired pneumonia, nosocomial *Candida* infections, HIV, tuberculosis and *Cryptococcus* meningitis as infections for which treatment guidelines were developed based on thorough studies. Endorsing the completeness of these types of guidelines and the sufficiency of their use as a standard reference in determining the appropriateness of prescriptions given for the treatment of these infections, the authors indicated that deviations from these guidelines may result in treatment failures and increased costs. Commenting further on the usefulness of treatment guidelines as tools for appropriate prescribing, the authors cautioned against blind reliance on them for this purpose as exceptions to treatment guidelines do exist (Thompson & Wright, 1998:1003). They expressed the need for prescribers to identify infecting pathogens and their sensitivities to antibiotics in settings of other infectious diseases before prescribing the drugs. The extent to which prescribers do this contribute to appropriateness of antibiotic prescribing and they should for this reason, form integral components of instruments designed for assessing the appropriateness of antibiotic prescriptions. By these observations complete reliance on antibiotic prescribing guidelines as sole instruments for use in assessing the appropriateness of antibiotic prescriptions, are considered to be disadvantaged. They lack means of determining how prescribers establish presence of bacterial pathogens to justify their prescribing of antibiotics or predicting how effective prescribed antibiotics are going to be in treating the clinical condition in question. Establishing the effectiveness of drugs prescribed in the treatment of clinical conditions as Aronson (2004: 230) commented on, is of utmost importance in the evaluation of the appropriateness of prescriptions.

Dependence on expert judgement on appropriateness of prescription has been popularly used in assessing the appropriateness of antibiotic prescriptions by a number of researchers. This is evidenced by the 6 out of 8 studies reviewed above for which researchers were seen to use this means of assessing the appropriateness of antibiotic prescriptions (Thuong *et al.*, 2000: 501,502; Erbay *et al.*, 2009:53; Martinez *et al.*,

2007:235; Trap & Hansen, 2002:883; Alves da Cunha *et al.*, 2003:8; Akkerman *et al.*, 2005:570). Of these six (6) studies, the panel of experts in two of them based their judgements on literature derived information and/or recommendations in treatment guidelines (Thuong *et al.*, 2000:501&502; Trap & Hansen, 2002:883). Though prescription assessment decisions based on judgements of panels of experts seemed to be most preferably used by researchers, they also can not be said to have no shortcomings. Trap and Hansen (2002:883) reported difficulties in obtaining agreement and consistency in the scorings of the panel they employed in their assessment of prescriptions. According to their report it was much easier to obtain consensus on diagnoses where co-trimoxazole prescription was irrational compared with when an acceptable or rational choice of the drug was made. Use of a panel of experts in the assessment of antibiotic appropriateness, though not reported by any of the studies reviewed, has added disadvantages of increasing research costs. They are also not applicable to studies conducted in clinical environments where such experts are not available to be engaged. Use of experts in procedures of prescription assessments may not for these reasons be acceptable for use in clinical environments with neither the experts nor the funding of their engagement for these types of researches.

The developments of either MAI or PAI as instruments for measuring appropriateness of prescriptions were based on extensive literature search by the researchers. Except for criticisms on weightings given for an appropriateness assessment question for either of the instruments, their review by an editor of the Clinical Journal of Pharmacology was favourable (Aronson, 2004: 230). Similar instruments like the MAI or PAI on the basis of their cost and the non involvement of infectious disease experts in their development are envisaged to be more affordable for adoption in carrying out antibiotic prescription assessment studies in clinical environs where funding and availability of infectious disease experts may be a problem. Akkerman *et al.* (2005:570) did not report the use of experts in the development of instruments for the assessment of prescriptions in their study as described above. They used guidelines instead of literature derived information in assessing the appropriateness of antibiotic prescriptions in their study as reported. They were however able to categorise their studied prescriptions into various categories of appropriateness in line with their study objective. In general a lay out of the Akkerman is found desirable for this study and is adopted with a modification that included the use

of literature derived information in designing an instrument for assessing the appropriateness of antibiotic prescriptions as used in developing MAI.

2.7 Chapter summary

Literature on bacterial pathogens as aetiological agents of many infections as well as antibiotics was reviewed in this chapter. The morphological characteristics of various bacterial pathogens, mechanisms of their pathogenesis, infectious diseases associated with them and also their sensitivity patterns to commonly used antibiotics had particularly been given attention. The review on antibiotics similarly focused on the characteristics of the agents and included principally their classifications, their mechanisms of action and their therapeutic uses. Principles of appropriate prescribing of antibiotics and methods researchers commonly use in assessing the appropriateness of antibiotic prescriptions had also been covered. In the next chapter, the methodology of the study is presented.

CHAPTER THREE

3.0 RESEARCH METHODOLOGY

3.1 INTRODUCTION

The chapter presents details of the design and procedures followed in the conduct of this research which, as detailed below, was carried out in three phases.
Due to its nature and extent, the research was designed and conducted in three phases. Each phase addressed a group of specific objectives and included in the diagrammed framework of procedures shown in Figure 3.1:

- Phase I: Antibiotic prescription pattern study and treatment outcome evaluation and costing in in- and outpatients
- Phase II: Determination of antibiotic sensitivity patterns of isolated bacterial pathogens
- Phase III Investigating factors contributing to irrational prescription of antibiotics.

Flow charts that summarise and provide frameworks of procedural steps followed at each phase are presented at the beginning of procedure descriptions of each indicated phase. Data collection tools for the indicated phases were developed and tested in pilot studies designed for each phase of the study for their appropriateness and finalisation. Data collected were summarised and analysed in accordance with procedural details outlined for the individual phases as described in paragraphs that follow. All statistical analyses were performed using Microsoft Excel® 2007 and Statistical Analysis Systems® SAS for Windows 9.1® Terms or expressions necessary for interpretation of this chapter have been defined in section 3.6 at the end of this chapter. These include the following: **appropriate / inappropriate / appropriateness, adherence/non-adherence; absolute or definite/possible or suspected aetiologies or causative agents; case; condition of patient; costs of antibiotic prescriptions; costs of hospitalisation; criterion (plural criteria); days of hospitalisation; effects; rational/irrational prescribing of antibiotics; study site; site/anatomical site of infection; total cost of treating infection; treatment success rate (TSR); and treatment outcome.**

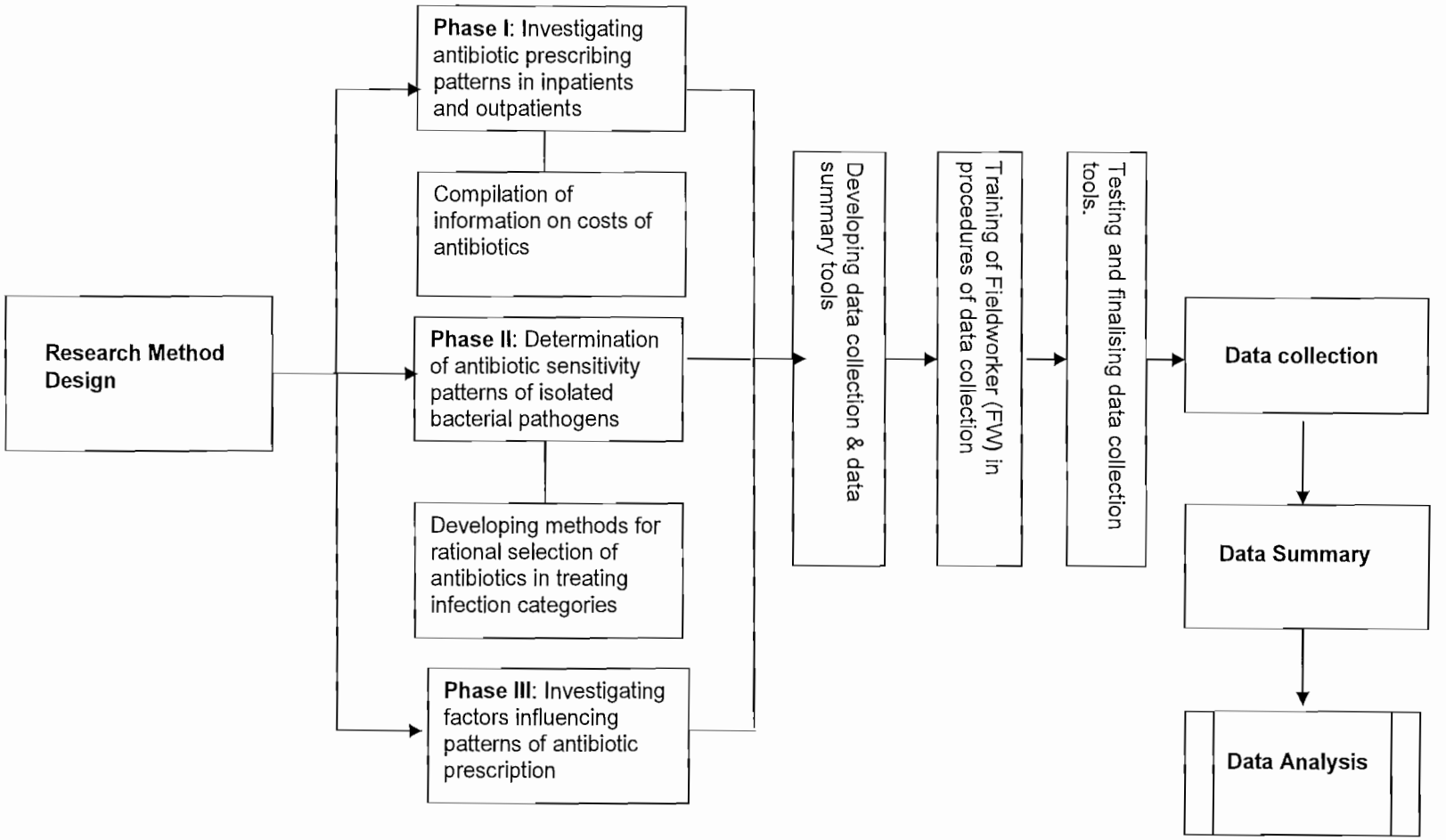

Fig 3.1: Framework of general procedural steps in the conduct of all phases of the study

3.2 Training of Fieldworkers

Fieldworkers (FWs) or research assistants (RAs) were trained in the data collection processes and employed in collecting data for the various phases of the research. Nine students of the Pharmacy Department of the National University of Lesotho were given two days training by the researcher in the use of tools designed for the collection and summarisation of data in Phases I, II and III of the study.

Four of the nine students were final year students who were given a more intensive training in the

- interpretation of inpatient case notes; and
- identification and use of relevant parameters in the therapeutic monitoring of inpatients' response to antibiotic therapy.

These four fieldworkers were mostly involved in data collection in hospital wards. The rest of the trained students and staff of pharmacies in outpatient departments of study site hospitals who were equally trained in the use of outpatient data collection tools like the students, were involved in collecting data in the other phases of the study. Competency of the fieldworkers and validity of data collected were ensured by the researcher's periodic visits to study sites every three days to validate data collected by RAs in his absence.

3.3 Empiric research Phase I: Antibiotic prescribing pattern study in inpatient and outpatient departments.

Prescriptions collected from both inpatient and outpatient departments of study sites were assessed and analysed for their appropriateness at this phase of the study in procedural steps outlined in the diagrammed framework shown in Figure 3.2. Assessed prescriptions were categorised into degrees of appropriateness with respect to prescribers' adherence to principles of antibiotic prescribing. Prescriptions were analysed to establish patterns of antibiotic prescribing in accordance with specific objectives as outlined.

3.3.1 Research objectives

The specific research objectives for study Phase I were as follows:

- **For both inpatient and outpatient settings**
  - To establish the extent to which antibiotics were prescribed appropriately in inpatient and outpatient settings in public health institutions in Lesotho through prescribers' adherence to principles of antibiotic prescribing.

- To establish infections commonly diagnosed and antibiotics most frequently prescribed in their treatment in both inpatient and outpatient departments.
- To predict effectiveness of established patterns of antibiotic prescribing in treating infections.
- To determine in terms of monetary value the proportions of prescribed antibiotics wasted on account of their inappropriate prescribing for cases identified as not having infections.
- To determine the extent of multiple prescribing of antibiotics in inpatient and outpatient settings.

- **For inpatient settings only**
  - To determine the impact of appropriateness of antibiotic prescribing on treatment outcome, days of hospitalisation and costs of antibiotic treatment.
  - To determine in terms of monitory value the proportions of prescribed antibiotics wasted on account of their inappropriate prescribing for cases identified as not having infections.
  - To predict effectiveness of established patterns of antibiotic prescribing in preventing post-surgical wound infections in patients.
  - To determine the impact of multiple prescribing of antibiotics on treatment outcomes in inpatient settings.

- **For outpatient settings only**
  - To determine prescriber qualifications involved and their abilities in prescribing antibiotics appropriately in outpatient departments.
  - To determine the impact of antibiotic stock unavailability on prescribers' choice of antibiotics in outpatient departments.
  - To determine the extent to which prescribers establish patients' need for antibiotics before prescribing the drugs in outpatient departments.
  - To evaluate the extent of accuracy of prescriber diagnosed infections and the effects of same on appropriateness of antibiotic prescribing in outpatient departments.

Details of procedures followed are as presented in paragraphs that follow.

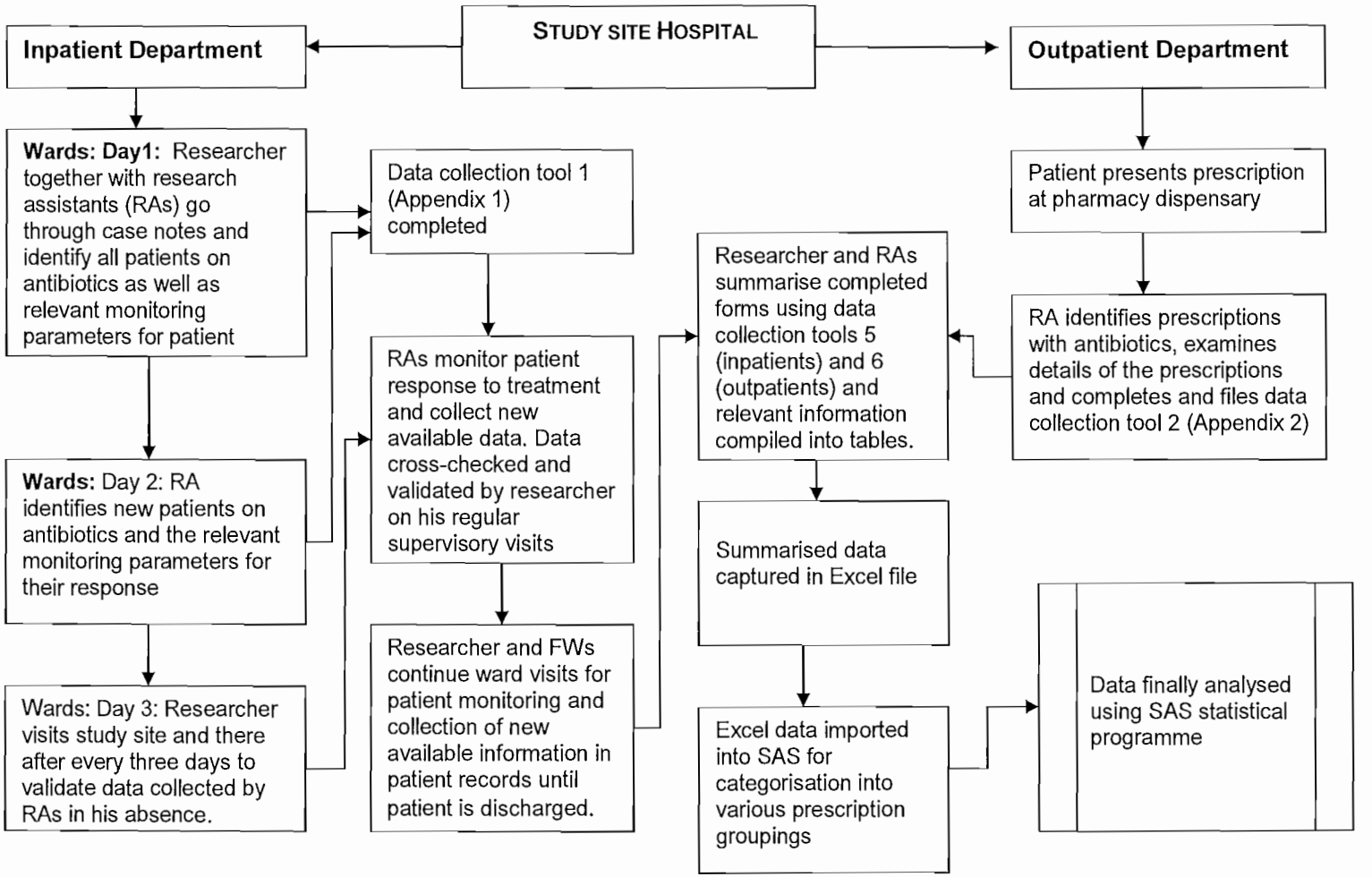

Fig 3.2 Empirical research Phase I: Framework of procedures of data collection and analysis in antibiotic prescribing pattern study

3.3.2 Study site selection

Five Health Service Area (HSA) Hospitals comprising three Government and two CHAL Hospitals were selected for the study by using criteria stipulated in Chapter 1, section 1.5.2. The two types of hospitals operate under different administrative bodies and hence different operational policies. Differences in such administrative or operational policies were thought to differently affect drug prescriptions generally and antibiotic prescribing specifically in patient care. The decision to select both Government and CHAL hospitals for this study took cognisance of this and is intended to provide a means of generating data which, when analysed, would produce a pattern of antibiotic prescribing more reflective of the country situation. The Queen II Hospital, apart from its being the largest hospital in Lesotho in terms of bed size, is the national referral hospital to which cases beyond the scope of management of district hospitals are referred. Its inclusion among the selected sites of study along with the Motebang Hospital, the second largest hospital in the country, is anticipated to promote the generation of data from a case mix considered quite representative of the country situation at all hospital levels.

3.3.3 Developing data collection tools and procedures of data collection and prescription categorization

3.3.3.1 Developing data collection tools

Data collection tools 1 and 2 (Appendices 1 and 2) were developed and tested in pilot studies for their suitability in the collection of data on case reports of individual patients treated for infections in both inpatient and outpatient patients. They were found suitable following the initial pilot study after necessary corrections and alterations to their subject content and relevance had been made.

3.3.3.2 Sources of data and procedures of data collection

- **Inpatient prescription records**

Inpatient antibiotic prescriptions (N = 307) emanating from study sites within one month period spanning from June 15 to July 15, 2006 were studied and relevant data as detailed in data collection tool 1 were collected (Figure 3.2.). Medical records of patients

on admission in both medical and surgical wards at each study site hospital during the specified study period were examined by both researcher and fieldworkers. Data were collected in the manner stipulated in the framework using indicated data collection tool. Patients' responses to antibiotic treatments were monitored prospectively by using objective and/or subjective monitoring parameters. Patients whose medical records were entered into the study but who were not discharged on or before July 15 2006 were continued to be monitored for the relevant data collection till the end of their hospital stay.

- **Outpatient prescription records**

Data on outpatient antibiotic prescriptions (N = 865) were collected from patients' medical booklets or "bukanas" from June 15 to July 15, 2006, same data collection period as for inpatients. The "bukanas" were examined as patients presented them at study site hospital pharmacies for their prescribed medications. Data were collected from all patients for whom antibiotics had been prescribed. Data collection tool 2 was used for this purpose.

Where prescribed antibiotics were not available patients were returned to prescribers for second choice antibiotics to be prescribed for them. Patients for whom prescribers insisted on their given choices of prescribed antibiotics to be dispensed, were asked to buy such prescribed antibiotics from retail pharmacies.

3.3.3.3 Classification of antibiotic prescriptions

A procedure that involved examination of prescriptions to establish whether or not a prescriber followed literature documented principles (Archer & Polk, 2005:795-797; Chambers, 2001:1146, Guglielmo, 2008:56-1) in prescribing antibiotics either empirically or based on culture sensitivity test results for treatment or prophylaxis of infections, was used to classify all antibiotic prescriptions into categories. Seven prescription categories defined as shown in Table 3.1 were created and included prescription categories A1, A2, B, C, D, E and F.

By these definitions

- **Category A1** prescriptions included prescriptions that were empirically written appropriately in accordance with principles of antibiotic prescribing for the treatment of infections for which bacteria pathogens were absolute aetiologies;

- **Category A2**, prescriptions that were empirically written appropriately in accordance with principles of antibiotic prescribing for the treatment of clinical conditions in which bacteria pathogens may be possible aetiologies;
- **Category B**, prescriptions that were empirically written for the treatment of infections but considered inappropriate on the basis of prescribers not adhering to the principles of antibiotic prescribing;
- **Category C**, prescriptions for which prescribed antibiotics were selected and prescribed based on available results of culture sensitivity tests;
- **Category D**, prescriptions of antibiotics that were empirically prescribed for the prevention of infections but considered appropriate on the basis of prescribers adhering to the principles of appropriate antibiotic prescribing;
- **Category E**, prescriptions that were empirically prescribed for the prevention of infections but considered inappropriate on the basis of prescribers' non-adherence to the principles of antibiotic prescribing; and
- **Category F**, which embodies prescriptions which, additional to prescribers not adhering to the principles of antibiotic prescribing, were empirically written for conditions for which uses of antibiotics were not justified.

3.3.4 Criteria development for prescription assessment.

Criteria conceptually developed from guiding principles of antibiotic prescribing as documented in the literature (refer to Section 2.3.3) and listed in Tables 3.2 and 3.3 were phrased into tabular formatted questionnaires (Appendixes 3 and 4; Data collection tools 3 and 4). Entries of "Yes", "No" or "Not applicable" responses to questions embodied in the questionnaires when a given treatment record for a given patient was assessed, produced data that were analysed to establish the appropriateness of antibiotics prescribed for the patient in question. All patient records originating from inpatient and outpatient departments were examined. Data summarisation tools 3 and 4 (Appendices 3 and 4) were completed to produce two separate sets of data that were analysed to determine the appropriateness and hence the classification of antibiotic prescriptions emanating from the two departments into categories as defined in Table 3.1. Examples of prescriptions as classified into respective prescription categories are shown in Appendix 5.

Table 3.1: Summary of prescription category definitions

Characteristics used in categorising prescription appropriateness	Prescription categories and conformities to appropriateness characteristics						
	A1	A2	B	C	D	E	F
Degree of appropriateness	Appropriate	Appropriate	Inappropriate	Appropriate	Appropriate	Inappropriate	Inappropriate.
Reason for prescribing	Treatment of infection	Treatment of infection	Treatment of infection	Treatment of infection	Prevention of infection	Prevention of infection	Use of antibiotic not justified
Principles adhered to	Yes	Yes	No	Not applicable	Yes	No	No
Presence of pathogens absolute	Yes	No	No	Yes	Not applicable	Not applicable	Not applicable
Prescribed empirically	Yes	Yes	Yes	No	Yes	Yes	Yes
Culture sensitivity tests performed	No	No	No	Yes	Not applicable	Not applicable	Not applicable

Table 3.2: Criteria for determining appropriateness of antibiotic prescriptions for inpatients (Formulated from principles of antibiotic prescribing outlined in Section 2.3.3)

Criterion	Criteria used
1	Suggestive signs and symptoms of infection present
2	Presenting signs and symptoms absolute for bacterial infection
3	Site of infection or possible site for infection identified
4	Potential source of infection e.g. indwelling catheter and prosthetic devices or surgical and other open wounds present
5	Presence of infection established by or objective data
6	Presence of infection inferred from symptoms only
7	Antibiotic prescribed alone
8	Initial antibiotic treatment modified by addition of other antibiotics
9	Initial antibiotic treatment modified by substitution of other antibiotics
10	Prescribed doses of antibiotic/antibiotics correct
11	Antibiotics in multiple therapy compatible
12	Spectra of activity of 2 or more antibiotics in multiple antibiotic therapy similar
13	Prescribed antibiotic (s) indicated against all possible pathogens associated with site of infection
14	Bacterial morphological and Grams stain before therapy initiation
15	Culture sensitivity test ordered before antibiotic therapy initiation
16	Culture sensitivity test performed in the course of antibiotic therapy
17	Antibiotic choice based on culture sensitivity test results

Table 3.3: Criteria for determining appropriateness of antibiotic prescriptions for outpatients (Formulated from principles of antibiotic prescribing Section 2.4.3)

Criterion	Criteria used
1	Suggestive signs and symptoms of infection present
2	Presenting signs and symptoms absolute for bacterial infection
3	Site of infection or possible site for infection identified
4	Potential source of infection e.g. indwelling catheter and prosthetic devices or surgical and other open wounds present
5	Presence of infection established by objective data
6	Presence of infection inferred from symptoms only
7	Antibiotic prescribed alone
8	Prescribed dose of antibiotic correct
9	Antibiotics in multiple therapy compatible
10	Spectra of activity of 2 or more antibiotics in multiple antibiotic therapy similar
11	Prescribed antibiotic (s) indicated against all possible pathogens associated with site of infection
12	Bacterial morphological and Grams stain determined before therapy initiation
13	Culture sensitivity test performed before initiation of or during antibiotic therapy
14	Antibiotic choice based on culture sensitivity test results

A table indicating the diagnoses or symptoms of infections and a summary of literature reviewed on such infections to establish their aetiologies was compiled. This was used as a tool (Appendix 6) in the data compilation procedures in making decisions on whether or not diagnoses or symptoms for which antibiotics were prescribed were of bacterial causes.

The concept of developing indicated criteria emanated from a line of thought in which it was postulated that antibiotics can be considered appropriately or rationally prescribed if literature propounded basic principles of antibiotic prescribing are followed (refer to Section 2.3.3). The selection of criteria developed into instrument used in the assessment procedure was done purposely to enable appropriateness evaluations of prescriptions from the perception of antibiotics being prescribed both

- justifiably in established cases of need for antibiotic prescriptions; and
- appropriately either alone or in combination with other antibiotics to ensure their effectiveness in treating infections.

Antibiotic cost considerations as a desired principle to be adhered to in appropriate prescribing of antibiotics was not used in developing criteria employed in assessing the appropriateness of antibiotic prescriptions. The type and severity of infections or the existence of concurrent clinical conditions along infections, may determine antibiotic choices and their preferred formulations in treating a given infection. Antibiotic cost considerations in such instances may not be an ardent principle determining the appropriateness of prescribed antibiotics.

.

3.3.4.1 Rationale for criteria development

The rationale for criteria development and the justifications for their use in the prescription assessment procedures are outlined below as follows:

- **Presence of signs and symptoms suggestive of infection: (Criterion 1; Tables 3.2 and 3.3)**

The presence of an absolute sign or a hallmark of infection indicates the presence of an infection and provides a means of establishing the presence of an infection to justify the prescription of an antibiotic (Guglielmo , 2008: 56-1).

- **Consistency of presenting symptoms with that of bacterial infection: (Criterion 2; Tables 3.2 and 3.3).**

The consistence of the symptoms of a presenting clinical condition with that of bacterial infection is suggestive of the presence of bacterial infection and justifies an antibiotic prescription.

- **Site of infection: (Criterion 3; Tables 3.2 and 3.3)**

Certain pathogens are more associated with infections at certain body sites than others (Guglielmo, 2008: 56-1). Identifying a site of infection in empiric antibiotic prescription in principle provides a means of both establishing the presence of an infection and selecting antibiotics that will appropriately target the most likely infecting pathogens.

- **Potential source of infection and prophylactic use of antibiotics: (Criterion 4; Tables 3.2 and 3.3)**

Signs and symptoms of an infection may not manifest in a patient at the time the patient is seen but the presence of potential sources of infection in the patient e.g. indwelling catheters, prosthetic devices, open wounds, or clinical conditions that increase patients' risks for contracting infections e.g. urinary retention, immuno-suppression (e.g. in neutropenic patients), etc., may justify prophylactic use of an antibiotic in the patient (Drew, 2008:68-1, 68-2, 68-4). In assessing the rationality of an antibiotic prescription it is necessary therefore to use criteria that establish whether in the absence of a currently established infection antibiotics have been justifiably prescribed for prophylactic use due to an established potential source of infection in the patient.

- **Establishing presence of infection by objective data: (Criterion 5; Tables 3.2 and 3.3)**

In situations where the presence of an infection is established by objective data in a patient the prescription of an antibiotic in no uncertain terms will be justified. Microscopic examinations of stained specimens provide both information on the presence or absence of an infection and a clue on antibiotic susceptibility to enable appropriate antibiotic selection for treatment of infection. Additional to microscopic examinations of specimens, other laboratory tests like polymorphonuclear leukocyte counts and also results of X-rays of body organ can be used to confirm diagnosis and hence establish presence of

infection to justify antibiotic prescriptions (Guglielmo, 2008: 56-1, 56-2, Gelone & O'Donnell, 2008:60-6).

- **Clinical presentation as a basis for antibiotic prescription: (Criteria 5 & 6; Tables 3.2 and 3.3)**

Clinical presentations are most of the time used as a basis for antibiotic prescriptions in outpatient departments as evidenced by a number of studies. Malcolm and Marrie (2003: 799) noted 21% (163 out of 768) of their study subjects in a study in which they investigated antibiotic therapy for ambulatory patients with community acquired pneumonia in an emergency department setting, being prescribed antibiotics on presentations. Steinman *et al.* (2003: 719) similarly reported 1257 out 1981 patients visiting clinics among study subjects they investigated for "*predictors of broad spectrum antibiotic prescribing for acute respiratory tract infections in adult primary care*" being prescribed antibiotics on presentation. The similarities of symptoms of certain bacterial infections with non-bacterial infections or clinical conditions result in the prescription of antibiotics in cases that actually are not bacterial infections. Such cases include, for example, the prescription of antibiotics for respiratory viral infections (Gonzales *et al.*, 2001:491) or chronic obstructive airways disease with symptoms of chronic cough and excessive production of sputum (Gelone & O'Donnell, 2008:60-2). Vulvovaginal symptoms caused, for example, by retained foreign bodies, e.g. tampons, vaginal spermicides, vaginal douches or allergic reactions to latex condoms which may demonstrate as discharges similar to vaginal discharges of bacterial aetiology, (Holmes, 2005: 768) may end up being treated with antibiotics. In assessing the rationality of antibiotic prescriptions therefore there is need to ascertain that where clinical presentation is used as a determinant of the presence of an infection it must absolutely be for bacterial infections.

- **Number of antibiotics prescribed: (Criteria 6 and 10: Table 3.2 and Criteria 7 and 9: Table 3.3)**

Apart from producing combined effects which could not be different or synergistic, the prescribing and concurrent use of two antimicrobial agents according to Guglielmo (2008:56-23) could produce antagonistic effects reflecting as the combined effects of the two prescribed antibiotics being less than the sum of the effects of either antibiotic prescribed alone. An example of such antagonism that the author indicated, is the combination of imipenem with a less β-lactamase stable β-lactam antibiotic such as

piperacillin. By way of explanation, the author further stated that when β-lactamase producing organisms are exposed to imipenem and piperacillin, the β-lactamase degrades and inactivates the piperacillin and antagonism results. Based on this, the assessment of the correctness of an antibiotic prescription should include a consideration as to whether the antibiotic has been prescribed alone or in combination with other antibiotics. If prescribed in combination, the appropriateness of the antibiotic prescription must be determined on the basis of what effects the prescribed antibiotics have on each other in respect particularly to whether or not the prescribed antibiotics are compatible and do not inhibit or antagonise the effects of each other.

- **Modification of antibiotic regimens in the course of antibiotic therapy: (Criteria 7 and 8; Table 3.2).**

Modification of antibiotic prescriptions done in hospitals should be guided by results of culture sensitivity tests (Chambers, 2001:1146) and not on the basis of trial and error. In assessing the rationality of antibiotic prescriptions for inpatients, it is deemed essential to formulate criteria that would assess the basis for any modification of prescribed antibiotics that was done during the course of treatment.

- **Prescribed doses of antibiotics: (Criterion 9: Table 3.2 and Criterion 8: Table 3.3)**

Incorrect dose of a prescribed antibiotic is a harbinger of treatment failure. The dose and dosing regimens of antibiotics have traditionally been selected to achieve antibacterial activity at the site of infection for most of the dosing interval of the antibiotic without any show of toxicity to host cells (Chambers, 2001:1160). In cases of changes in the pharmacokinetic parameters of the individual patient such traditional doses of the antibiotic can lead to its accumulation to toxic levels in much the same way as if it were given in an "overdose". This may occur particularly in patients with renal or hepatic failures or even in the elderly with compromised renal function in whom drug clearance can be significantly reduced further according to Chambers (2001:1160). Such considerations become very important when considering antibiotics with narrow therapeutic windows. Imipenem is known to be associated with seizures particularly in patients with renal failure and in doses in excess of 50mg/kg/dose and must be prescribed at lower doses in patients with kidney failure or patients with epilepsy (Guglielmo, 2008:56-14). Gentamicin, the author further indicated, may similarly have to be given to elderly patients with reduced renal function in less than what is the traditional

dose of the antibiotic to avoid its aminoglycoside nephrotoxicity and ototoxicity adverse effects. An antibiotic when appropriately prescribed on account of these reasons must be prescribed in correct doses for a given patient, taking into consideration patient factors that could lead to changes in the pharmacokinetic properties of the antibiotic. It is important, hence, that in assessing the rationality of antibiotic prescriptions it is necessary to include a criterion for dosage evaluation.

- **Spectra of activity of antibiotics: (Criteria 11 and 12: Table 3.2 and Criteria 10 and 11: Table 3.3)**

Antibiotics with similar spectra of activity, except if synergistic or capable of preventing the emergence of resistant mutants of pathogens in their combined effects, may offer no therapeutic advantage in the treatment of infections if prescribed together. This is inferred from conditions under which combined antibiotic chemotherapy can be employed according to Archer and Polk (2005:797). In principle the spectrum or combined spectra of activity of antibiotic(s) empirically prescribed in treating a given infection should cover all pathogens implicated as possible aetiological agents of that infection to ensure an effective treatment of the infection. Any two or more antibiotics prescribed together for this reason should have their additive spectra of activity covering all target pathogens possibly causing the infection to be considered appropriately prescribed. In support of these statements, Chambers, (2001:1146) opinion on the issue of antibiotic coverage in empirical prescribing of antibiotics is quoted. According to the author, "when used as empirical or initial therapy, the antibiotic must 'cover' all of the likely pathogens since the infecting organism(s) has not been identified" and that "combination therapy or treatment with a single broad spectrum often is employed".

Literature information on spectra of activity of commonly used antibiotics in Lesotho was compiled (Appendix 7) and used in the assessment process. The spectra of activities of antibiotics prescribed together were interpreted on the basis of their antibacterial activities against target pathogens associated with infections for which they have been prescribed. Prescribed together, for this reason, the antibiotics must be seen according to principle to broaden each others spectrum of activity or seen to be synergistic Ciprofloxacin and nitrofurantoin for example have different spectra of activity when their literature documented spectra of activity are considered (Appendix 7). In the context of this research the two drugs may be taken as having similar spectra of activity when prescribed together in urinary tract infections where Gram negative aerobic bacilli are

considered the target pathogens and their prescription together for the treatment of urinary tract infections will be considered inappropriate on the basis of this. According to Elliot (2004:191) the use of two antibiotics must broaden the spectrum of antimicrobial cover in principle. Examples the author gave were the justifiable use of cefuroxime and metronidazole to cover coliform organisms and anaerobes in treating abdominal sepsis and the prescribing together of gentamicin and penicillin for their synergistic effects.

- **Bacterial morphology and Gram's stain characteristics of infecting Pathogens: (Criterion 13: Table 3.2 and Criterion 12: Table 3.3)**

Knowledge of bacterial morphology and Gram's stain characteristics are necessary in rational selection of antibiotics for targeting bacterial pathogens in empiric antibiotic therapy. Prescribers are in principle expected to request for this information from the laboratory through microscopic examination of stained specimens of materials containing the infecting organisms for purposes of presumptively identifying assaulting pathogens before they prescribe antibiotics empirically (Archer & Polk, 2005:795).

- **Culture sensitivity tests (CST): Time of ordering and use of results in rational antibiotic prescribing: (Criteria 13 and 14: Table 3.2 and Criterion 13: Table 3.3)**

Rational antibiotic therapy initiation in inpatient settings particularly should in principle be preceded by requests for culture sensitivity tests (CST) and modifications of the empiric antibiotic prescription done when results are made available (Archer & Polk, 2005:795). Exposure of pathogens to antibiotics before specimens are sent to the laboratory for CST may result in suppression of the growth and hence the identification of certain potential pathogens that might be implicated as causative agents of the infection. This makes it necessary in principle and in procedure to send specimens to the laboratory for CST before commencement of antibiotic treatment (Scottish Infection Standards and Strategies Group, 2003:282; Bronska *et al.*, 2006:137; Popa *et al.*, 2009:227).The principle is mainly applicable in inpatient settings where patients are closely monitored for their treatments and can have their empiric antibiotic treatments changed more easily. It may also be applied in outpatient settings in situations where antibiotic regimens are modified in closely monitored patients. Keeping to this principle has an impact on appropriate antibiotic prescribing and has for this reason been used as a criterion for assessing the rationality of the studied antibiotic prescriptions.

- **Basing antibiotic choice on CST results: (Criterion 16: Table 3.2 and Criteria 14: Table 3.3)**

Culture sensitivity tests are performed for the purpose of the prescriber being in a position to prescribe antibiotics that can effectively eradicate causative pathogens in an infection. Other factors being equal, choice of antibiotics for effective treatment of infections should be based on CST results if available (Archer & Polk, 2005:795). Whether or not this is done in principle in the prescription of antibiotics for infections in situations where CSTs have been ordered and the results are available, can be used as a criterion in assessing the rationality of antibiotic prescription based on CST results as employed in this study.

3.3.5 Antibiotic treatment outcomes and costs determinations

To determine antibiotic treatment outcome the following were used:

- Notations in nursing notes pertaining to a patient's status on discharge.
- Information on treatment outcomes for inpatients were obtained from patient charts.
- Outcomes of patient monitoring using parameters indicating signs and hence presence of infections or infectious diseases treated in patients. These included such signs of infections as pus production in skin and soft tissue infections (McCormack & Brown, 2008:67-6), colour or degree of purulence and/or increased production of sputum or intensities of coughing and pleuritic pains in diagnosed cases of lower respiratory tract infections, e.g. exacerbated chronic bronchitis and or pneumonia (Gonzales *et al.*, 2001:491; Gelone & O'Donnell, 2008:60-2 & 60-6) and temperature measurements in various infections demonstrating with fever (Guglielmo, 2008:56-2). Ambrose *et al.* (2001:2794) in a study in which they evaluated treatment outcomes, determined clinical response by comparing patients' baseline signs and symptoms of infection with those after therapy and then categorised treatment outcome as either cure or failure.

Treatment outcomes for inpatients were noted as

- **"Improved"** when nursing notes indicated that patient was discharged "feeling better" or "feeling well" or any such term indicating that the patient responded to treatment or when a patient was monitored and positive response to antibiotic treatment was established as abatement of indicated monitoring parameter;

- **"Not improved"** when a patient was monitored and negative response to antibiotic treatment was established as non-abatement of indicated monitoring parameter or when notes in the patient chart indicated that a patient was referred to another hospital due to non-response to treatment or when relatives requested for a patient to be discharged for them due to a worsening of patient's condition or patient's non-response to hospital management; and
- **"Died"** when a patient died.

Death of a patient on antibiotic treatment was not considered as non-response to administered antibiotics for reasons that other factors independent of the effectiveness of antibiotics used in treating the patient in the opinion of the researcher, may equally have contributed to the death. The state of the patient's condition at the time of admission and death of a patient from a condition unrelated to infection being treated are examples of such instances. Appreciating similar difficulties or dilemma of precise association of cause of death to a parameter of study in a research, Feikin *et al.* (2000:224) in their study of mortality from invasive pneumococcal pneumonia faced problems of precisely attributing death to a parameter of study. As a means of solving this problem they excluded from analysis of pneumonia deaths, deaths after 30 days in hospital to improve their chances that deaths they attributed to invasive pneumonia as a cause were indeed due to pneumococcal infection rather than other causes.

Data on costs of antibiotic treatment and days of hospitalisation in the case of inpatient records only, were also collected for each patient record studied using data collection tools 5 and 6 (Appendices 8 and 9). **Costs of antibiotic prescriptions** were computed as actual costs of prescribed antibiotics used in treating patients. **Cost of hospitalisation** of a patient was determined as the product of daily cost of hospitalisation and total number of days a patient spent in hospitalisation. This is charged as a flat rate but is considered to cover costs of chargeable services rendered to the patient while on admission. It excluded costs of other drugs that may be used in treating clinical conditions other than infections, costs of surgical procedures and costs of laboratory investigations not related to patient monitoring for response to antibiotic treatments. **Total costs of treating infection** for inpatients were computed as the sum total of costs of antibiotic treatment, costs of hospitalisation and cost of culture sensitivity tests where they were performed. Total cost of outpatient prescriptions were calculated as the totals of costs of prescribed antibiotics and costs of culture sensitivity tests where they were performed.

3.3.6 Data analysis of research Phase I

Responses to questions in data collecting instruments used for collecting data from patient charts were captured electronically and analysed by the Statistical Analysis Systems® SAS for Windows 9.1®. All prescription records were examined and classified into prescription categories defined in Table 3.1 according to the steps listed below:

- Examining each prescription record for set criteria it did or did not conform to.
- Defining conditions by criteria combinations. Eighteen (18) and seventeen (17) conditions, numbered I to XVIII (Table 3.4) and I to XVII (Table 3.5) were respectively defined for inpatient and outpatient prescriptions.
- Examining prescriptions record by record and allocating them to conditions by means of the Statistical Analysis Systems® SAS for Windows 9.1® (Tables 3.6 and 3.7).

3.3.6.1 Analysis of inpatient antibiotic prescription data

Inpatient antibiotic data were analysed to determine the extent to which antibiotics were appropriately prescribed based on prescribers' adherence to antibiotic prescribing principles. The possible impact that appropriate prescribing of antibiotics might have on infection management in inpatient departments was further determined. Details of procedures followed were as indicated below.

- **Determining percentage frequencies of antibiotic prescription categories**

The number of antibiotic prescriptions was analysed to determine percentage frequencies of antibiotic prescription categories as pooled records for all study sites and also according to individual study sites and ward types. (Results: Tables 4.1.1, 4.1.2 and 4.1.3)

- **Quantitative assessment of extent of appropriate prescribing of antibiotics in surgical and medical wards.**

Ratios of appropriately to inappropriately written antibiotic prescriptions for treatment of infections as classified for surgical and medical wards were determined and used to establish on comparative basis, extent of appropriate prescribing of antibiotics in medical and surgical wards for treatment of infections.

Table 3.4 Criteria combinations and their indications: INPATIENT DATA

Condition#	Criteria grouping	Indication
I	"Yes" for criteria 1, 2 and 3 or 5 (i)	Presence of infection or need for antibiotic use for treatment established
II	"Yes" for criteria 1, 3 and 5(ii) and "No" for 2 and 5(i)	Bacterial Infection may be present though not confirmed
III	"Yes" for criteria 3 and 4 and "No" for criterion 1	Need for antibiotic use for prophylaxis established
IV	"No" for 1, 2, 3, and5 (i) OR "No" for 1, 2, and 5 (i) and "NA" for 3	Presence of infection or need for antibiotic use for treatment **NOT** established
V	"No" for 1, 2, 3 and 4 OR "No" for 1, 2, and 4 OR "No" for 1, 2, 3 and 4 OR "No" for 1, 2, and 4 "NA" for 3	Need for antibiotic use for prophylaxis **NOT** established.
VI	"Yes" for 6, and 12 and "No" for 7 and 15 OR "Yes" for 6, and 13 and "No" for 7 and 15	Principles of empiric prescribing of single antibiotic for treatment followed.
VII	"No" for 6 and 11 and "No" for 7 and 15 and "Yes" for 10 and 12 OR "No" for 6 and 11 and "No" for 7 and 15 and "Yes" for 10 and 13 OR "No" for 6 and 11 and "No" for 8 and 15 and "Yes" for 10 and 12 OR "No" for 6 and 11 and "No" for 8 and 15 and "Yes" for 10 and 13	Principles of empiric prescribing of multiple antibiotics for treatment followed
VIII	"Yes" for 6 and "No" for 12	Principles of empiric prescribing of single antibiotic for treatment **NOT** followed
IX	"No" for 6 and 10 OR "No" for 6 and "Yes" for 11 OR "No" for 6 and 12	Principles of empiric prescribing of multiple antibiotics for treatment **NOT** followed
X	"Yes" for 15 and "No" f or 16	Principles of empiric prescribing of antibiotic(s) for treatment **NOT** followed
XI	"Yes" for 7 and "No" for 14, 15 and 16 OR "Yes" for 8 and "No" for 14, 15 and 16	Principles of empiric prescribing of antibiotic(s) for treatment **NOT** followed
XII	"No" for 9	Medication error in antibiotic prescribing
XIII	"Yes" for 6, 15, and 16 and "No" for 7 OR "Yes" for 6, 15, and 16 and "No" for 8 "Yes" for 6, 15, and 16 and "Yes" for 7 OR "Yes" for 6, 15, and 16 and "Yes" for 8	Principles of antibiotic prescribing based on CST results followed
XIV	"No" for 6 and 7 and "Yes" for 10, 15, and 16 OR "No" for 6 and 8 and "Yes" for 10, 15, and 16 OR "No" for 6 and "Yes" for7,10,15 and 16 OR "No" for 6 and "Yes" for 8,10,15 and 16	Principles of antibiotic prescribing based on CST results followed
XV	"Yes" for 3 and 4 and 6, and 12	Principles of antibiotic prescribing in prophylaxis followed
XVI	"Yes" for 3 and 4 10, 12 and "No" for 6 and 11	Principles of antibiotic prescribing in prophylaxis followed
XVII	"Yes" for 3 and 4 and 6 and "No" for 12	Principles of antibiotic prescribing in prophylaxis **NOT** followed
XVIII	"Yes" for 3 and 4 and "No" for 6 and 10 OR "Yes" for 3, 4 and 11 and "No" for 6 OR Yes" for 3, and 4 and "No" for 6 and 12	Principles of antibiotic prescribing in prophylaxis **NOT** followed

Table 3.5 Criteria combinations and their indications: OUTPATIENT DATA

Condition#	Criteria grouping	Indication
I	"Yes" for criteria 1, 2 and 3 OR "Yes" for 5	Presence of infection or need for antibiotic use for treatment established
II	"Yes" for 1, 3, and 6 and "No" for 2 and 5 OR "Yes" for 1, and 6 and "No" for 2, 3 and 5	Bacterial Infection may be present though not confirmed
III	"Yes" for criteria 3 and 4 and "No" for 1	Need for antibiotic use for prophylaxis established
IV	"No" for 1, 2, 3 and 5 Or "No" for 1, 2, and 5 and "NA" for 3	Presence of infection or need for antibiotic use for treatment NOT established
V	"No" for 1, 2, and 4 and "NA" for 3 OR "No" for 1, 2, 3 and 4	Need for prophylactic use of antibiotic NOT established
VI	"Yes for 7 and 11 OR "Yes" for 7 and 12	Principles of empiric prescribing of single antibiotic for treatment followed
VII	"No" for 7 and 10 and "Yes" for 9 and 11 OR "No" for 7 and 10 and "Yes" for 9 and 12	Principles of empiric prescribing of multiple antibiotics for treatment followed
VIII	"Yes" for 7 and "No" for 11	Principles of empiric prescribing of single antibiotic for treatment NOT followed
IX	"No" for 7 and 9 OR "No" for 7 and "Yes" for 10 OR "No" for 7 and 11	Principles of empiric prescribing of multiple antibiotics for treatment NOT followed
X	"Yes" for 13 and "No" f or 14	Principles of empiric prescribing of antibiotic(s) for treatment NOT followed
XI	"No" for 8	Medication error in antibiotic prescribing
XII	"Yes" for 7, 13, and 14	Principles of antibiotic prescribing based on CST results followed
XIII	"No" for 7 and "Yes" for 9, 13, and 14	Principles of antibiotic prescribing based on CST results followed
XIV	"Yes" for 3, 4, 7, and 11	Principles of antibiotic prescribing in prophylaxis followed
XV	"Yes" for 3, 4, 9, 11 and "No" for 7 and 10	Principles of antibiotic prescribing in prophylaxis followed
XVI	"Yes" for 3, 4 and 7 and "No" for 11	Principles of antibiotic prescribing in prophylaxis NOT followed
XVII	"Yes" for 3, 4 and 10 and "No" for 7 and 9 OR "Yes" for 3, 4 and 10 and "No" for 7 and 11	Principles of antibiotic prescribing in prophylaxis NOT followed

Table 3.6 Inpatient prescription rationality categorization

Prescription. category	Category definition	Conditions applying to prescription
A1	Antibiotic empirically prescribed in accordance with principles of antibiotic prescribing for the treatment of infection	Conditions I and VI OR Conditions I and VII apply
A2	Antibiotic empirically prescribed in accordance with principles of antibiotic prescribing for the treatment of possible infection	Conditions II and VI OR Conditions II and VII apply
B	Antibiotic empirically prescribed for the treatment of infection without adherence to the principles of antibiotic prescribing	Conditions I and VIII OR Conditions I and IX. OR Condition1 and X OR Conditions I and XI apply Conditions II and VIII OR Conditions II and IX. OR Conditions II and X apply. Condition I OR Condition II OR Condition IV OR Condition VI OR Condition VII OR Condition VIII OR Condition IX OR Condition X ONLY applies
C	Antibiotic prescribed based on culture sensitivity test results	Condition XIII OR Condition XIV apply
D	Antibiotic prescribed in accordance with the principles of antibiotic prescribing for the prevention of infection	Conditions III and XV OR Conditions III and XVI apply
E	Antibiotic prescribed without adherence to the principles of antibiotic prescription for the prevention of infection	Conditions III and XVII OR Conditions III and XVIII OR Conditions III and XVIII apply Condition III OR Condition XVII OR Condition XVIII ONLY applies
F	Antibiotic empirically prescribed without adherence to principles of antibiotic prescribing and in conditions for which antibiotic prescriptions are not justified	Condition IV OR Condition V
	Medication error	Condition XII = MEDERROR

Table 3.7 Outpatient prescription rationality categorization

Prescription Category	Category definition	Conditions applying to prescription
A1	Antibiotic empirically prescribed in accordance with principles of antibiotic prescribing for the treatment of infection	Conditions I and VI or Conditions I and VII apply
A2	Antibiotic empirically prescribed in accordance with principles of antibiotic prescribing for the treatment of possible infection	Condition II and Condition VI or Condition II and Condition VII apply
B	Antibiotic empirically prescribed for the treatment of infection without adherence to the principles of antibiotic prescribing	Condition I and VIII. or Condition I and IX. or Condition I and X apply Conditions II and VIII OR Conditions II and IX. OR Conditions II and XI apply. Condition I OR Condition II OR Condition IV OR Condition VI OR Condition VII OR Condition VIII OR Condition IX OR Condition X ONLY applies
C	Antibiotic prescribed based on culture sensitivity test results	Condition XII or XIII. applies to prescription
D	Antibiotic empirically prescribed in accordance with the principles of antibiotic prescribing for the prevention of infection	Condition III and XIV. or Condition III and XV apply
E	Antibiotic empirically prescribed for the prevention of infection without adherence principles of antibiotic prescribing.	Condition II and XVI OR Condition II and XVII apply
F	Antibiotics empirically prescribed without adherence to principles of antibiotic prescribing and in conditions for which antibiotic prescriptions are not justified	Condition IV Or Condition V

Theory

Knapp (1985:54) in his book "Basic statistics for nurses" written more than 20 years ago, defined "ratio" in a way found most relevant to understanding procedures of analysis of results of this section of the study and is quoted here in absence of newer editions of this book. According to Knapp (1985:54), the definition of the ratio of the occurrence of one event, to the occurrence of some other event, indicates the number of times the one event occurs relative to the other event occurring once. (Indicated reference by the researcher's search of the literature gave the most appropriate definition of "ratio" as used as basis for determinations shown below). Applied to this determination, appropriately prescribing an antibiotic prescription in a given ward is one event and inappropriately prescribing it another. A ratio of the relative frequency of antibiotic prescriptions classified as appropriate to the relative frequency of those classified as inappropriate by the above definition of ratios defines the chances of an antibiotic prescription being appropriately written for every chance that it is inappropriately written. Determining and using such ratios provide a means quantitatively assessing and comparing the extent to which antibiotics are appropriately written in given patient care environments. Formula used in the calculation is given as

$$R = (A1 + A2)/(B+F)$$

where R is the ratio of percentage frequencies of appropriately to inappropriately written prescriptions, (A1+A2) the sum total of percentage frequencies of categories A1 and A2 prescriptions and (B+F) similarly the sum totals of percentage frequencies of categories B and F prescriptions.

- **Determining the impact of appropriate or inappropriate prescribing of antibiotics on treatment outcomes, days of hospitalisation, and cost of antibiotic treatment**

Prescription categories were analysed according to study sites, diagnosis, treatment outcomes, average days of hospitalisation and average and total costs of treatment to determine any differences in these parameters among defined prescription categories. [Results: Tables 4.1.4.1 through 4.1.4.4 refer].

- **Determining the impact of extents of appropriateness of antibiotic prescribing on treatment outcomes**

The effects that appropriateness of antibiotic prescribing have on antibiotic treatment outcomes were determined by calculating and comparing relative therapeutic success rates (refer to next paragraph) among patient groups receiving antibiotics for treatment and for whom antibiotic prescriptions were seen to be written

- appropriately for absolute bacterial infections (Prescription category A1);
- possible bacterial infection (prescription category A2);
- inappropriately prescribed (prescription category B) and
- based on culture sensitivity tests results (prescription category C).

- **Calculating treatment success and relative treatment success rates**

Treatment success rate (TSR) is defined as the rate at which a patient group receiving antibiotic treatment responds positively to such treatment. It was determined for total patient population receiving antibiotics for treatment and expressed as a range between two values to accommodate instances where death, though considered not necessarily an indicator of no response to antibiotic therapy (Section 3.3.5) may in fact be attributable to patients' non-response to therapy.

The lower TSR value for the range was calculated as

- percentage ratio of patients to whom antibiotics were given for treatment and categorised as "improved" (I) to the total number of patients receiving antibiotics for treatment and categorised as "improved (I), "not improved (NI) and "Died" (D) according to their response to treatment $\{(TSR_{(lower)} = [I / (I + NI + D)]*100\}$

The upper TSR value for the range was similarly calculated as:

- percentage ratio of patients to whom antibiotics were given for treatment and categorised as "improved (I), to the total number of patients receiving antibiotics for treatment and categorised as "improved (I) and "not improved (NI) according to their response to treatment $\{(TSR_{(upper)} = [I / (I + NI)] * 100\}$. Calculated TSR for group of patients receiving treatment was expressed between the lower and upper values as "$TSR_{(lower)}$ - $TSR_{(upper)}$ "

TSR of antibiotic treatments in patient groups treated with prescription categories A1, A2, B, and C and designated $TSR_{(A1)}$, $TSR_{(A2)}$, $TSR_{(B)}$, and $TSR_{(C)}$, were determined within lower and upper ranges as indicated above. Relative treatment success rates (RTSR) were calculated as ratios of treatment success rates of subgroup of patients treated with given antibiotic prescription categories to treatment success rate of the total population of patients receiving antibiotic treatment. They were determined at both levels of TSR range and expressed as an average value as shown below using TSR values for patient group treated with antibiotic prescriptions categories A1.

$$RTSR_{(A1)} = \frac{TSR_{(A1)lower}}{TSR_{(lower)}} - \frac{TSR_{(A1)upper}}{TSR_{(upper)}}$$

Expressed as average of lower and upper values:

$$RTSR_{(A1)} = \frac{\frac{TSR_{(A1)lower}}{TSR_{(lower)}} + \frac{TSR_{(A1)upper}}{TSR_{(upper)}}}{2}$$

Determinations of RTSRs for sub-patient groups treated with respective antibiotic prescription categories enabled the expression of calculated sub-patient treatment success rates on a unified linear scale. This allowed an easier comparative assessment of the extent of antibiotic treatment successes in the respective patient groups and hence a determination of the impact of appropriate antibiotic prescribing on treatment outcomes (Results: Table 4.1.5 refers).

- **Determining the impact of appropriateness of antibiotic prescribing on days of hospitalisation**

The impacts of appropriateness of antibiotic prescribing on days of patients' hospitalisation was determined by comparing differences in average number of days spent in hospital by patient groups treated with antibiotics prescribed empirically on prescription categories A1 and A2 on one hand and prescription category B on the other hand. The impacts of appropriate and inappropriate prescribing of antibiotics on days of hospitalisation were determined by

- determining percentage frequencies of categories A1, A2, and B prescriptions for diagnosed infections excluding records of patients who died; and

- comparing averages of days of hospitalisation of patients admitted for various diagnosed infections.

- **Determining percentage frequencies of diagnosed infections according to prescription categories for data excluding records of patients who died**

Data sorted for prescription categories A1, A2 and B and patient recovery status of "improved" and "not improved", were used for purposes of excluding records of patients who died. This exclusion was found necessary on the basis of the variable "Days of hospitalisation" being interpreted from the perspective of patients' recovery in shorter or longer periods of antibiotic use. Death of a patient obliterates this effect of the use of an antibiotic in treating a patient.

- **Determinations of effects of diagnosed infections on days of hospitalisation.**

Average days of hospitalisation of patient groups diagnosed or not diagnosed with given infections were determined. Effect sizes for differences between groups of patients diagnosed or not diagnosed for days of hospitalisation were calculated and interpreted to indicate effects of diagnosis on days of hospitalisation (Results: Table 4.1.6.3 refers).

- **Determining the impact of appropriate and inappropriate prescribing of antibiotics on costs of antibiotic treatment**

- Average costs of antibiotics prescribed per prescription in each category were compared to determine variations in the effects of appropriateness of antibiotic prescribing on costs of antibiotic treatments (Results: Table 4.1.7 and 4.1.8 refer)
- Effect sizes (d-values) were determined for differences in both average costs of antibiotic prescriptions and total average costs of treating infections for patient groups treated with prescription categories "A1 and A2", "A1 and B" and "A2 and B". Calculated d-values were interpreted to ascertain practical significance of observed differences in the average costs of antibiotic treatment of indicated patient groups.

- **Determining cost of antibiotic wastage in inpatient departments through unwarranted prescribing of antibiotics**

Percentage cost of antibiotics wasted (PCAW) on account of their being prescribed for clinical conditions in which bacterial infections were absolutely not aetiologies during the period of study was calculated as percentage ratio of costs of category F

prescriptions to the total costs of antibiotic prescriptions given appropriately or inappropriately for all clinical conditions treated as infections. Mathematically, percentage cost of antibiotics wasted was determined from the expression PCAW = Cost of Category F prescriptions / the sum of costs of categories A1, A2, B, C and F prescriptions (Results: Tables 4.1.7 and 4.1.8 refer).

- **Determining patterns and effects on treatment outcomes of multiple antibiotic prescribing in wards**

Analysis of prescriptions was done to determine the extent of prescribers' use of multiple antibiotic therapies in treating infections; associations of multiple antibiotic therapies with appropriateness of antibiotic prescribing; and effects of single and multiple antibiotic therapies on antibiotic treatment outcomes.

- **Determining the extent of multiple antibiotic prescribing and associations of same with appropriateness of antibiotic prescribing**

  - Prescriptions were analysed to determine the extent to which prescribers use multiple antibiotics in the treatment of infections among inpatients at study sites.
  - Associations between number of prescribed antibiotics and appropriateness of antibiotic prescribing were determined (Results: Table 4.1.9 refers).

- **Determining effects of single and multiple antibiotic therapies on antibiotic treatment outcomes**

Relative treatment success rates of antibiotic treatment among patients receiving single antibiotic therapy were determined and compared to establish any differences in the curative rates of infections treated with single and multiple antibiotic therapies in which antibiotics were appropriately or inappropriately prescribed based on principles of antibiotic prescription writing. Upper range treatment success rate determinations in which patients who died in the course of their treatment were excluded from totals of patients treated with indicated prescription categories were used in relative treatment rate determinations (Results: Tables 4.1.11.1, through, 4.1.11.4 refer).

- **Determining most commonly prescribed antibiotics for given clinical conditions**

Lists of prescriber indicated diagnoses, symptoms and symptom complexes indicating presence of infections, clinical conditions indicating potential sources of infections and

clinical conditions not indicative of bacterial infections but for which antibiotics were prescribed were compiled from patient case notes and sorted into groups of clinical conditions collectively designated as infections at given anatomical sites. These include as listed below.

Group 1: Respiratory tract infections
Group 2: Gastrointestinal tract infections
Group 3: Genitourinary infections
Group 4: Skin and soft tissue infections
Group 5: Bone infections
Group 6: Central nervous system infections
Group 7: Blood infections
Group 8: Pyrexia of unknown origin
Group 9: Diagnoses non-indicative of bacterial infections

- **Determining patterns of antibiotic prescribing in and response rate for post-surgical antibiotic prophylaxis**

Relevant frequency tables generated from subset data sorted for antibiotic prescriptions for post-surgical prophylaxis were analysed to determine number and types of antibiotics often prescribed in post-surgical antibiotic prophylaxis at study sites. Post-surgical antibiotic therapy success rate (PostSurg-ATSR) was determined from the expression:

PostSurg-ATSR = [RT / (RT +NRT)][100];

where RT and NRT respectively represent number of patients responding and not responding to therapy for post surgical antibiotic prophylaxis. Calculated post-surgical antibiotic therapy success rate was interpreted to reflect the degree of success of prophylactic antibiotic use at study sites.

3.3.6.2 Analysis of outpatient antibiotic prescription data

Procedures followed are detailed as follows:

- **Determining outpatient antibiotic prescribing patterns, and prescription categories according to prescriber qualifications**

Tables of percentage frequency distributions of prescription categories according to study sites and prescriber qualifications on the other hand were generated and analysed to establish percentage proportions of doctors and nurse clinicians contributing to the different types of prescription categories at respective study sites (Results: Figure 4,1.7 & Tables 4.1.21 and 4.1.22 refer).

- **Determining the impact of appropriateness on antibiotic prescribing on average costs of outpatient antibiotic prescriptions, the extent to which antibiotics are singly or multiply prescribed**

Prescription categories according to study sites and average and total costs of treatment were analysed to determine any differences in costs of antibiotics among defined prescription categories. The extents to which antibiotics are singly or multiply prescribed in outpatient departments were similarly determined (Results: Table 4.1.24 and 4.125 refer).

- **Determining effects of drug availability as factor on prescribers' choice of antibiotics in outpatient departments**

Prescribers' choices of antibiotics were analysed according to study site, to determine whether or not such choices were made based on availability of antibiotics of choice. These were done to determine chances of prescribers' first choice antibiotics being available upon prescription and hence extents to which antibiotic availability determines prescribers' alternate choices of antibiotic (Results: Table 4.1.26 refers).

- **Determining whether prescribers established the need for antibiotic use or the presence of infections prior to prescribing antibiotics in outpatient departments**

Prescriptions were analysed according to prescribers' use of antibiotic need assessment criteria in order to establish the extent to which prescribers ascertain need for antibiotic use or presence of infections in outpatient settings prior to prescribing antibiotics (Results: Table 4.1.27 refers).

- **Determining leading infections observed in outpatient settings of study sites and antibiotics most commonly prescribed for their treatment**

Prescribed antibiotics were analysed according to diagnosed infections at study sites to determine leading infections observed in outpatient settings of study sites and antibiotics most commonly prescribed for their treatment (Results: Tables 4.1.28 through 4.1. 34 4.1.29, refer).

3.4 Empiric research Phase II: Antibiotic prescribing pattern study in inpatient and outpatient departments.

A flow chart of procedures followed in the collection and analysis of data for determining antibiotic sensitivity patterns of bacterial isolates as shown in Figure 3.4.

3.4.1 Research objectives

The specific objectives of research Phase II include the following:

- To determine the extent of bacterial pathogen isolations at study sites.
- To determine and provide a list of bacterial pathogens associated with commonly diagnosed infectious diseases in Lesotho for adequate antibiotic coverage in empiric treatments of infections.
- To determine sensitivity patterns of bacterial pathogens to prescribed antibiotics.
- To determine any changes in bacterial sensitivity patterns to given antibiotics over past five years preceding period of sensitivity data collection.
- To develop easily applicable procedure for the rational antibiotic selection in the treatment of infections based on available data on frequencies of isolation of pathogens from given specimens, their sensitivities to formulary antibiotics and the costs of antibiotics indicated for the treatment of their infections.

3.4.2 Culture sensitivity database generation

A flow chart of procedures followed in the collection and analysis of data for determining antibiotic sensitivity patterns of bacterial isolates is shown in (Fig 3.4). Records of culture sensitivity test results (N = 5007) dating from January 2000 to June 2006 from all five study sites were examined and relevant data on the sensitivities of isolated organisms to

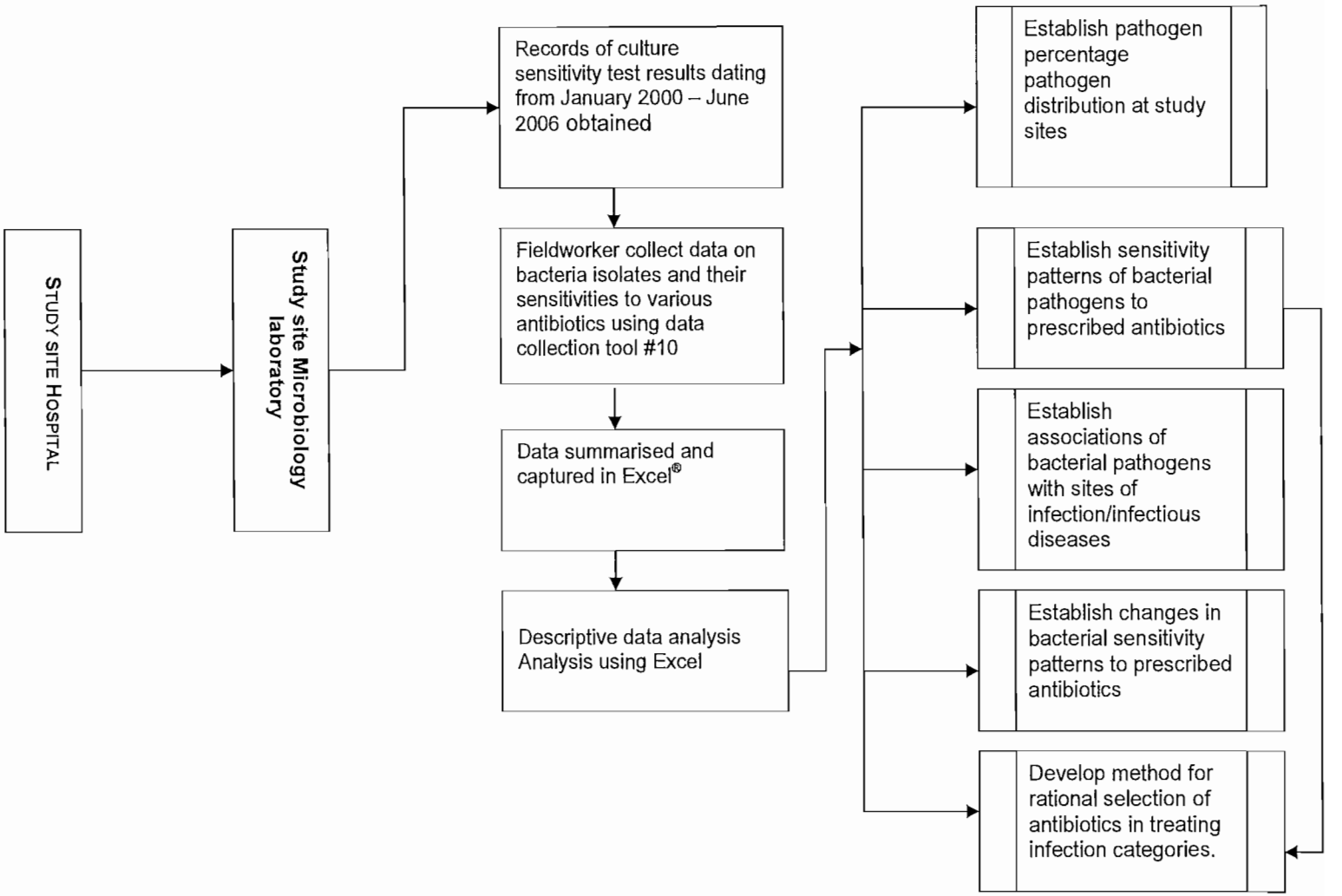

Fig 3.3 Empirical Research Phase II: Framework of procedures of data collection and analysis in determining bacterial isolate sensitivity patterns

antibiotics against which they were tested were collected using pre-designed data collection tools (Appendix 11).

Information was specifically gathered on bacteria pathogens that were explicitly identified by their individual biological names or by their species in cases where isolated organisms were identified so by the laboratory.

Data were collected specifically on

- specimen types from which pathogens were cultured; and
- degrees of bacteria isolate sensitivities to antibiotics against which they were tested.

Data on isolates identified only by their morphological and gram staining characteristics were excluded. Data collected were manually summarised using various data summary and tallying forms designed for the purpose and then organised in tabular formats to indicate sources, frequencies of isolation and sensitivity patterns of individual isolated pathogens to prescribed antibiotics.

3.4.3 Analysis of culture sensitivity results data

- **Establishing sensitivity patterns of bacterial pathogens to prescribed antibiotics**

Isolation and culture sensitivity testing data of bacterial pathogens and their sensitivities or resistances to given antibiotics were determined as percentage ratios of the number of times isolates were found sensitive or resistant to such given antibiotics to the total number of times they had been tested against the given antibiotics, were compiled and analysed.

- **Establishing associations of bacterial pathogens with sites of infection and/or infectious diseases**

Data on pooled percentage frequencies of isolation of pathogens from various specimens from study sites were summarised and tabulated. Histograms of percentage frequencies of occurrence of isolated pathogens were constructed for each specimen and inferences thereof made on pathogens that were observed to be most commonly associated with the given specimens.

- **Establishing changes in bacterial sensitivity patterns to prescribed antibiotics**

Pooled data on the frequencies of testing and percentage yearly resistances of pathogens to given antibiotics were determined as percentage ratios of the number of times isolates were found sensitive or resistant to given antibiotics in a given year to the total number of times they had been tested against the given antibiotics in that year, were tabulated for the years Jan to Dec 2000 through Jan to Dec 2005. Culture sensitivity test results data for organisms that were isolated and tested each year over the indicated time period of data collection were used for the analysis. Calculated percentage resistances of pathogens in the year Jan to Dec 2000 were taken as baseline. Average percentage resistance rates of an organism to a given antibiotic from 2001 to 2005 were calculated. These were compared with the baseline percentage resistance recorded for year 2000. Differences that showed whether or not there had been an increase or decrease in the resistance of the pathogen to the antibiotic over the five year period following the baseline year were determined.

3.5 Procedures of selecting antibiotics in empiric treatment of infections

A method based on percentage (%) overall activities, therapeutic success to failure ratios and costs of antibiotics demonstrating varying degrees of effectiveness against associated pathogens of a particular infection as shown by results of culture sensitivity tests on specimens associated with infections have been developed and used for selecting antibiotics to be used in infections for which specimens are routinely investigated for their microbial contents and antibiotic sensitivities currently in Lesotho. The following paragraphs outline the logical reasoning and mathematical steps used in developing the formula as well as relevant applications generally in antibiotic selections in infections being considered.

The multiplication rule of probability can be used to determine the probabilities of two separate events occurring together simultaneously. In stating this rule Turner and Knighton (1989:271) and Utts and Heckard (2007:246) indicated that if A and B are two separate events, then A∩B (read as A intersect B) or P(A and B) represents the event of both A and B taking place at the same time. The authors further indicated that where A and B are independent events then the probability of A and B occurring simultaneously equals the product of their individual probabilities of occurrence, i.e. P(A∩B) or P(A and

B) = P(A)P(B). Since the incidence of isolation of a pathogen from a specimen and its sensitivity to an antibiotic are independent events, it is postulated from these quoted laws of probability that the incidence or probability of an organism being isolated from a specimen and it being sensitive to a given antibiotic at the same time is the product of the probabilities of isolation of the pathogen from the specimen and its sensitivity to the given antibiotic. This practically gives the probability of an empirically selected and prescribed antibiotic being effective against a given pathogen. This postulate was used to develop a formula for calculating the probabilities of a prescribed antibiotic being effective against common isolates from a given specimen. This is referred to as "Percentage Overall activity" (POA) and is based on organisms' percentage frequencies of isolation from that specimen and their sensitivity data to various antibiotics (Blondeau & Tillotson, 1999: 147).

3.5.1 Developing formula for calculating percentage overall activity (POA) of given antibiotics

The following information is assumed to be available for developing formula for calculating POAs of given antibiotics against all possible bacterial isolates in a specimen from first principles.

Pathogens A, B and C were isolated from Specimen Z. Their respective percentage frequencies of isolation (PFI) and sensitivities (PS) to antibiotic 1, 2 and 3 were determined and presented as shown below (Table 3.8).

Table 3.8 Example of Table showing pathogen frequency and sensitivity values for formula derivation.

Pathogen	PFI	Percentage sensitivity(PS) to antibiotics		
		Antibiotic 1	Antibiotic 2	Antibiotic 3
A	25	90	70	70
B	25	80	90	60
C	50	70	80	40

The probability (P) of a pathogen being isolated from a given specimen {incidence of isolation [$P_{(i)}$] = PFI/100)} and it being sensitive to a given prescribed antibiotic {incidence of sensitivity [$P_{(s)}$] = PS/100} is given by

$$P = P_{(i)} \cap P_{(s)}$$

Consider Antibiotic 1

Probabilities of pathogens A (P_A), B (P_B) and C (P_C) being isolated from Specimen Z and their being sensitive to antibiotic 1 are respectively given by:

$$P_A = P_{(iA)} \cap P_{(sA)}$$
$$P_B = P_{(iB)} \cap P_{(sB)}$$
$$P_C = P_{(iC)} \cap P_{(sC)}$$

where $P_{(iA)}$ $P_{(iB)\ and}$ $P_{(iC)}$ are probabilities of isolation of pathogen A, B, and C from specimen Z and $P_{(sA)}$ $P_{(sB)}$ and $P_{(sC)}$ their respective probabilities of being sensitive to antibiotic 1. P_A, P_B and Pc are probabilities of Antibiotic 1 being active against individual pathogens A, B and C if present in the specimen. The sum total of these probabilities expressed as a percentage fraction of the Total incidences of isolation gives the probability of Antibiotic 1 being active against all possible pathogens. This is termed percentage overall activity of Antibiotic 1 against possible pathogens implicated as aetiological agents of the infection. It is calculated from the relationship according to (Bordeaux & Tillotson, 1999: 147)

$$\textbf{\%Overall activity (Antibiotic}_1\textbf{)} = [P_{(iA)} \cap P_{(sA)} + P_{(iB)} \cap P_{(sB)} + P_{(iC)} \cap P_{(sC)} / P_{(iA} + P_{(iB)} + P_{(iC)}]^* 100$$

Example of calculations using above formula for derivation of the POAs of antibiotics 1, 2 and 3 against all three pathogens are as shown in Table 3.9 below. Based on these calculations Antibiotic 2 is the most probable to be effective against all three pathogens followed by Antibiotic 1 and lastly Antibiotic 3

Table 3.9. Example Table showing calculated probabilities and POAs of antibiotics against isolated pathogens

Pathogen	PFI	$P_{(i)}$	Pathogen sensitivities and Probabilities of Antibiotic activity against Pathogens $P_{(i)} \cap P_{(s)}$								
			Antibiotic 1			Antibiotic 2			Antibiotic 3		
			PS	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	PS	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	PS	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$
A	25	0.25	90	0.9	0.225	70	0.7	0.175	70	0.7	0.175
B	25	0.25	80	0.8	0.2	90	0.9	0.225	60	0.6	0.15
C	50	0.5	70	0.7	0.35	80	0.8	0.4	40	0.4	0.2
Total	100	1			0.775			0.8			0.525
POA = Total $P_{(i)} \cap P_{(s)}$/Total $P_{(i)}$ * 100			77.5			80			52.5		

3.5.2 Developing method for selecting an antibiotic of choice in treating a given infection.

Based on the basic principle of a prescribers' desire to select an antibiotic with highest treatment success rate at most affordable financial cost to patient or health institution and using combined information on antibiotics combined POAs and costs, a number of terms and formulae for calculating them have been developed. Concepts, reasoning and mathematical relationships that have been assumed and applied in developing these terms and the respective formulae for their calculations include:

- **Antibiotic treatment success rate (ATSR):**

  Antibiotic treatment success rate (ATSR) is a term derived in this study to represent the effectiveness of an antibiotic expressed as a quantified unit or entity. In meaning it denotes the probability or chances of using a given antibiotic in treating successfully an infection for which common isolates and their sensitivity patterns to a range of antibiotics including the given antibiotic are known.

° **Assigning value to ATSR**

The ATSR when a given antibiotic is used in treating that infection is assumed to be directly proportional to the POA of that antibiotic against possible pathogens associated with the infection. In other words, the POA of the antibiotic is the higher the chances of it being successfully used in treating the infection.

Mathematically this is expressed as

ATSR α POA ..... (1)

i.e.

ATSR = Constant * POA ..... (2)

♦ **Antibiotic treatment failure rate (ATFR)**

Antibiotic treatment failure rate (ATFR), unlike ATSR, is a term derived in this study to represent the ineffectiveness of an antibiotic expressed as a quantified unit or entity. It is the opposite of ATSR and denotes the probability or chances of failing to treat successfully an infection for which most probable offending pathogens and their sensitivities to given antibiotics including the antibiotic of reference are known. ATFR is assumed to be directly proportional to percentage overall resistance (POR) of pathogens to the given antibiotic.

° **Assigning value to ATFR**

When a pathogen is tested against a given antibiotic for an "x" number of times and is found to be sensitive to the antibiotic for "y' number of times, its PS, is determined as the ratio of "y" to "x" (y/x) multiplied by 100 and its percentage resistance (PR) as 100 - PS i.e., the ratio of "x-y" to "x" multiplied by 100. POA and POR resistance are directly linked respectively with PS and PR. Therefore

POR = 100 - POA ..... (3)

ATFR α POR ..... (4)

ATFR = Constant * POR ..... (5)

° **Relationship of ATSR and ATFR to POA and POR**

The proportionality constants of these relationships as could be experimentally determined will depend on characteristics attributable to both infection type and the antibiotic in question. For example the degree of concentration of antibiotic at site of infection will be a factor determining whether treatment will be successful or not. This in turn is dependent on pharmacokinetic and physicochemical properties of the antibiotic. For a given antibiotic used in a given type of infection these proportionality constants will be the same for both treatment success and treatment failure rate relationships with POA and POR resistance respectively. Based on this and dividing equation (2) by equation (5), the ratio of ATSR to ATFR can be determined from the relationship

$$ATSR/ATFR = POA/POR \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (6)$$

♦ **Antibiotic treatment success to failure ratio (ATSFR)**

The ratio, ATSR/ATFR is termed by these derivations as the **antibiotic treatment success to failure ratio (ATSFR).** It is a numeric factor that characterises the effectiveness of the antibiotic in terms of the number of chances when it is successfully used to treat given infection per chance of its failure to treat that infection. It can be determined and listed for all antibiotics that demonstrate degrees of effectiveness in treating a given infection. Its value is determined from

$$ATSFR = ATSR/ATFR \quad \ldots\ldots\ldots\ldots \quad (7)$$
$$= POA/POR \quad \ldots\ldots\ldots\ldots\ldots \quad (8)$$

♦ **Rationale of deriving ATSFR - Comments**

It is noted here as a way of clarification that though the ratio ATSR to ATFR is numerically equal to the ratio of POA to POR, the terms ATSR and ATFR are not synonymous to or the same as percentage overall activity or percentage overall resistance in meaning respectively. ATSR and ATFR are *in vivo* determinations derived from the concept of actually curing or failing to cure an infection when the antibiotic is used as equations 2 and 5 depict. POA and POR on the other hand are *in vitro* determinations that in ways are able to predict the success or failure of the antibiotic when it is used to treat an infection.

An antibiotic with a higher ATSFR will be preferred to one with a lower ATSFR if selection of the antibiotic is based only on its POA and POR resistance considerations. ATSFR can be considered as a "wanted characteristic" of the antibiotic.

The formula for determining ATSFR applies only in situations when an antibiotic does not have a 100% overall activity or a 0.0% overall resistance. In a situation where POA and POR are respectively equal to 100% and 0% ATSFR is equal to 100%/0.0% which mathematically is undeterminable. Much as this may be considered a limitation in the derivation and use of the formula, it does correctly depict the practical reality of the activity of antibiotics in practice. Because of varying characteristics of various types of bacteria pathogens associated with an infection with respect to their morphology, intrinsic sensitivities to antibiotics and mechanisms of resistance development to various antibiotics it is rather rare to have an antibiotic that demonstrates 100% overall activity towards all possible pathogens associated with an infection.

- **"Antibiotic selection factor" (ASF)**:

  The cost of an antibiotic is one of the major determinants of the overall cost of treating an infection and is an economic factor that is considered in the rational selection of an antibiotic from a group of antibiotics that could be possibly used in treating an infection. Cost of antibiotic for this purpose is calculated as cost of the quantity of the antibiotic normally prescribed for treating the infection in ambulatory patients (orally administered antibiotics) or as cost of a daily course of the antibiotic (parenteral preparations) prescribed in treating the infection in hospitalised patients. Cost is a characteristic of the antibiotic that has a negative impact on the choice of the antibiotic as a preferred antimicrobial agent in treating the infection. In other words, it is an "unwanted characteristic" of the antibiotic. To reflect the effect of cost of the antibiotic (an "unwanted characteristic") on its choice, its ATSFR ("wanted characteristic") is calculated as a per unit cost value, to provide a numeric value that defines the degree to which the cost of the antibiotic as a factor (an "unwanted characteristic") decreases and hence tend to invalidate its "wanted characteristic". In this study this numeric value is referred to as "**Antibiotic selection factor**"

(ASF). ASF can be calculated for all antibiotics which can be possibly used in treating a given infection and then used as one of the criteria in antibiotic selection.

ASF = ATSFR/cost of antibiotic ..... (9)

When two antibiotics generally are compared the one with a higher ASF will be selected over one with a lower ASF on basis of their cost.

- **Computing antibiotic selection factor" (ASF) from ATSFR and costs of antibiotics against which commonly isolated pathogens from a given specimen are tested**:

For illustration the following data (Table 3.10) are assumed to be available and were used to calculate ASFs for antibiotics A, B, C, D & E tested against possible pathogens associated with a given specimen, Specimen Z.

Table 3.10 Example of Table showing calculated antibiotic selection factors (ASFs)

Antibiotic	POA	POR = 100-POA	ATSFR = ATSR/ATFR	Cost of normally prescribed course of treatment (Maloti)	ASF = ATSFR/cost
A	90	10	9	11.9	0.76
B	80	20	4	9.66	0.41
C	70	30	2.3	1.68	1.4
D	60	40	1.5	19.60	0.07
E	50	50	1	7.28	0.14

3.5.3 Use of percentage overall activity characteristics and costs of antibiotics in the rational selection of the drugs

Using culture sensitivity test results of laboratory specimens evaluated for their microbial compositions and sensitivities to commonly prescribed or formulary antibiotics, POAs or ATSFRs and ASFs for formulary antibiotics were calculated from the above derived formulae. Appropriate tables of these values and corresponding antibiotics tested for their activities against bacteria isolates were constructed for various laboratory

specimens [Appendix 12(i) - 12(xiv]. Specimens by their nature are representative of infection categories and bacteria isolates identified with them the presumed common aetiological agents of the infections for which the specimens were taken.
List of available antibiotics with information on their formulation unit doses and costs and prescribed courses of treatment were compiled using data collection tool no. 7 (Appendix 10). Calculations of daily costs of each antibiotic as used in prescribed courses of treatment of infections were done and values obtained appropriately tabulated for use as source of data on antibiotic costs in the computation of ASFs (Appendix 13).

Calculated POAs and antibiotic selection factors ASFs *vis a vis* other factors that need to be considered in the selection of an antibiotic from a group of antibiotics in treating an infection, were used to select antibiotics that should be prescribed as first, second and third choices in the treatment of infections with which given specimens are associated.

- **Antibiotic selection procedures: Comments and suggestions**

Selection of antibiotics for treating infections is usually a prerogative of Hospital Therapeutic Committees and is guided by what policies such committees have in place to ensure efficacies of antibiotic treatments at least affordable costs to patients and institutions and to control the development of resistant bacteria. Depending on prevailing situations, the selection of antibiotics could be based only on the POA of the antibiotic against infecting pathogens or its ATSFR if that is a paramount consideration of the therapeutic committee. Alternatively, it could be based on costs and POA of the antibiotic or its ATSFR if costs of antibiotic treatment are a matter of concern to the committee. In other cases the committee can decide on rotating antibiotics for purposes of curbing the development of resistance of organisms to them or at least decreasing cross transmission of antibiotic resistance (Van Loon *et al.*, 2004:480), introducing changes in antibiotic use in the event of resistance development or restricting the use of particular antibiotics (Barbosa & Levy, 2000:307). In such cases POA and ASF characteristics may or may not be considered if a particular antibiotic only will have to be used in circumstances prevailing at the time. Proposed procedures of antibiotic selections in this study take cognition of these prevailing situations and accordingly put forward two procedures of antibiotic selections. These include:

- rational selection of an antibiotic based on the POA of the antibiotic against possible pathogens implicated in the infection; and
- rational selection of an antibiotic based on both POA and costs of the antibiotic in which cases the ASF will be the deciding factor in selecting the antibiotic.

The listings were procedurally done as follows:

- Maximum four antibiotics with POAs of more than 60% or more were selected
- For situations where antibiotic selection is based on both effectiveness and costs of the antibiotics, the antibiotic with the highest ASF among the four is listed as antibiotic of first choice followed in that order by antibiotics with second, third and fourth highest values of ASF. Antibiotic C in the example has the highest ASF. Its POA of 70 is high enough to ensure appreciable coverage of common pathogens and would hence be preferentially selected over the other antibiotics on the basis of its ATSFR and cost
- For situations where antibiotic selection is based on the effectiveness of the antibiotics only, the antibiotic with the highest ATSFR or POA among the four is listed as antibiotic of first choice followed in that order by antibiotics with second third and fourth highest values of ATSFR or POA. In the above example Antibiotic A will be selected as a first choice antibiotic for treating the infection. In the event of treatment failure in such cases culture sensitivity test results should form the basis of what antibiotic should be prescribed next in the management of the patient.

3.6 Empirical Research Phase III: Investigating factors influencing patterns of antibiotic prescribing in public health institutions in Lesotho

Data for this phase of the study was collected from a questionnaire survey conducted in December 2006 within HSAs of study site hospitals where data for study Phases I and II were collected. A framework representing general procedures employed in the collection and analysis of data for the phase of the study is shown in Figure 3.5.

3.6.1 Research objective

The primary objective of research Phase III was to establish factors contributing to established patterns of antibiotic prescribing in Lesotho. Specifically the following itemised issues were investigated to see the extent to which they serve as factors

determining established patterns of antibiotic prescribing in the country's hospitals. They include the following:

- Prescribers' levels of professional training, work experience, and workload.
- Availabilities and functional capabilities of support systems required in antibiotic prescribing.
- Influences of patient and prescriber related factors on prescribers' decisions to prescribe antibiotics.
- Extent to which prescribers adhere to principles of antibiotic prescribing.
- Prescribers' knowledge as a pre-requisite in appropriate prescribing of antibiotics.
- Costs of antibiotics and pathogen sensitivity pattern considerations in making appropriate choices of antibiotics.
- Reasons for prescriber's non-request for laboratory assisted information in appropriate prescribing of antibiotics.

3.6.2 Study population

All prescribers within Health Service Areas (HSAs) abounding the five (5) hospitals selected for this study were the target population of this study. Fifty one (51) questionnaires that were returned out of a total 67 distributed, were treated as a convenient sample out of the total population of prescribers targeted for the study.

.

3.6.3 Method of data collection

Collecting information in studies or surveys that involve society can be done through a number of means including data gathering from documentary sources, by observation and by questionnaires. Questionnaires are either mailed or hand delivered to respondents by the researchers or fieldworkers. The questionnaires can be self-administered or self-completed and returned to the researcher by postage or delivery to a set point for collection by the researcher, or are administered by the researcher in an interview session with the respondent (Bryman, 2004:132,167,380) or by a combination of any of these methods (Dawson, 2006:35).

In cases where the survey or study deals with what a person thinks or what his or her opinion is about a subject matter of interest, it does become necessary to collect

relevant data through asking people questions directly and relying on answers they provide as data to be analysed. Neuman (2006: 273) stated that surveys ask people about their beliefs, opinions, characteristics, and past and present behaviour and that they produce information that is statistical in nature. When questions are to be asked in data collection for such societal opinion based survey studies use of questionnaires that are either administered by direct or personal interviews or mailed to respondents for them to self-administer and return to the researcher is employed. Compared to direct interviewing, mail questionnaire methods have the advantage of cheapness and provides a more spread sample as wider geographical areas can be covered. It also gives respondents time to think and even check personal records if necessary to provide accurate or near accurate answers. The method also avoids interviewer bias that may introduce errors associated with the direct personal interviewing. Mail questionnaire methods are, however, seriously disadvantaged by difficulties of securing adequate response because people generally do not always complete and return questionnaires. Apart from this and other noted disadvantages of mail questionnaire survey methods, questionnaires may be returned uncompleted or in some cases completed by some one else other than the intended respondent (Neuman, 2006:299).

Information required for use as data for analysis in investigating most likely factors that influence the pattern of antibiotic prescribing within health service areas of study site hospitals involve collection of

- prescribers' opinions on what they think are factors that influence the way they prescribe antibiotics; as well as
- a determination of their display of knowledge in principles that guide their ways of prescribing antibiotics.

From the foregoing review of survey methods questionnaire administration was considered an appropriate method for use in collecting this type of data and was hence employed. Questionnaires were designed for the purpose in the structural format described in section 3.5.2 below. They were tested in a pilot study as indicated in the framework diagrammed for the general procedures for the study. They were found suitable for use in data collection after necessary alterations to their subject content and relevance had been made based on results of analysis of the pilot data and questions raised by participants of the pilot study.

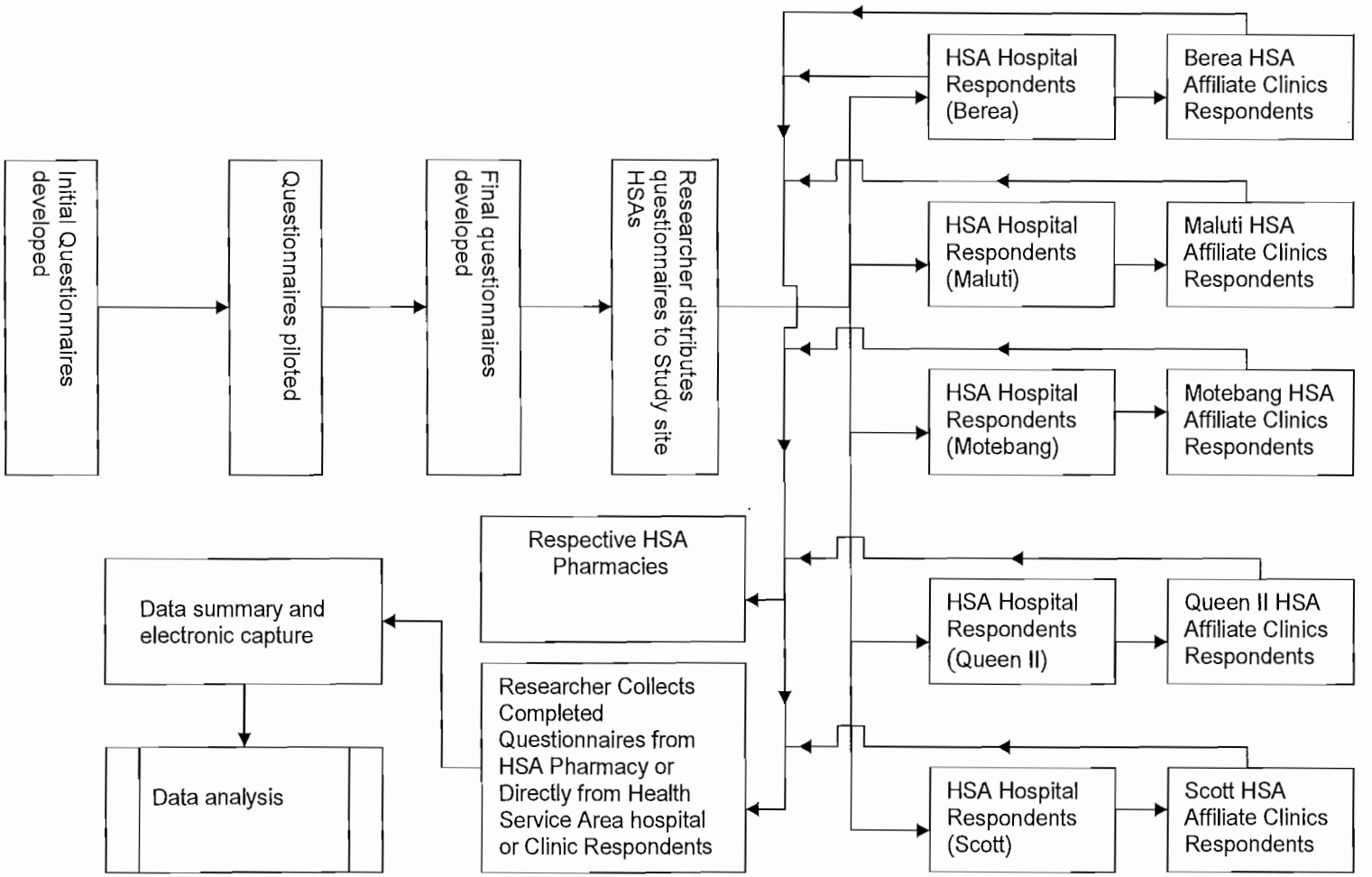

Fig 3.4 Empirical research Phase III: Framework of Questionnaire development and administration

3.6.4 Structuring of questionnaires, rationale of question formulation and purposes of questions

- **Method of data collection**

Questionnaires used in the data collection were structured in a closed-ended or pre-coded format with respondents limited to a number of answers or statements expressing their opinions to choose from (Appendix 14). The order of questions largely followed the pattern provided by Aldrigde and Levine (2001:115). Questions seeking information on particulars of respondents and their practice environments (Question 1 – 8) which were straight-forward and relatively easy to answer were asked first, assumingly to put respondents at ease and make them more comfortable to answer questions. This was followed by questions that sought to investigate possible factors that might influence patterns of antibiotic prescribing (Question 9), including testing prescribers' knowledge in areas of interest pertaining to antibiotic prescribing (Question 11).

Part I

Particulars of prescribers and their practice environments (Questions 1-8)

Respondents' qualification, their years of working experience and workloads in terms of number of patients they see in a day, patient types they treat and also the availability of functional microbiology laboratories that are needed for the provision of diagnostic and bacterial pathogen identification services are all factors that will influence patterns of antibiotic prescribing.

Part II

Investigating the degree to which patient and prescriber related factors influence prescribers' decisions in the prescription of antibiotics (Question 9)

Questions embodied in this part of the questionnaire were designed to

- investigate the extent to which respondents are influenced by a number of listed factors and their perceptions about antibiotic use; as well as
- effects of expressions patients are likely to make regarding their illnesses and what treatments they expect to receive for them.

Part III

Investigating prescriber habits in the prescribing of antibiotics in outpatient departments (Question 10)

Questions in this section of the questionnaire were structured to determine how often respondents prescribe antibiotics in manners suggested by a list of statements that included prescribing antibiotics

- based on their suspicion of the presence of infections judging for patient's presenting signs and symptoms [Question 10(i)];
- following their positive establishment of an infection after they had physically examined the patient [Question 10(ii)];
- following their positive establishment of an infection through laboratory investigations [Question 10(iii)]; and
- even if they are not sure of their diagnosis or presence of infections [Question 10(iv)].

Stating either "never", "sometimes" or "always", respondents were asked to indicate how often they do what statements implied. Data collected were used to construct frequency tables of indicated response variables and then analysed to determine what prescribers do most in outpatient departments as they prescribe antibiotics, as well as degrees to which they prescribe antibiotics in conformity with the fundamental principle of antibiotic prescribing. Results obtained were used to predict expected patterns of antibiotic prescribing in outpatient departments based on prescribers' antibiotic prescribing habits and compared in discussion with patterns of antibiotic prescribing established from results of outpatient prescription analysis in study Phase I.

Part IV

Investigating the extent to which principles of rational antibiotic prescribing are adhered to in the prescription of antibiotics for inpatients (Question 11).

All study site hospitals have functional microbiology laboratories to facilitate pathogen identification and the determination of antibiotic sensitivity patterns of bacterial pathogens in the course of infection treatment. Respondents in these practice environments would for this reason be ordinarily expected to prescribe antibiotics following principles that are based on the use of microbiology laboratories. Such principles were formulated into activities and listed as

- send specimen to laboratory and request for rapid microscopic identification of pathogens before starting antibiotic treatment;
- send specimen to laboratory for culture sensitivity tests before initiating empiric antibiotic therapy;
- send specimen to laboratory for culture sensitivity tests only in the event of treatment failure;
- revise antibiotic treatment by replacing initially prescribed antibiotics with antibiotics to which organisms are sensitive; and
- revise antibiotic treatment by adding antibiotics to which organisms are sensitive to initially prescribed antibiotics.

Answering "Yes", "No", or "At times", respondents were asked to indicate whether or not they performed listed activities as they prescribe antibiotics. Relevant frequency tables of indicated response variables were constructed and analysed to determine extents to which respondents abide to or violate these principles as they prescribe antibiotics and hence to predict patterns of antibiotic prescribing or the appropriateness of such prescriptions in inpatient settings. Results were compared with established patterns of inpatient antibiotic prescribing at study sites as determined in Phase I of this research and relevant conclusions were made.

Part V

Assessing prescribers' knowledge in principles of antibiotic prescribing (Questions 12 – 19).

Prescribers' knowledge in principles of appropriate prescribing of antibiotics which among other things would include their knowledge of

- the nature of the infection;
- the morphological characteristics;
- antibiotic sensitivity patterns of the various bacterial pathogens likely to cause such infection; and
- the cost of a selected antibiotic

are essential basic determinants of their ability to correctly prescribe empirically given antibiotics for the treatment of given infections.

It is considered a major factor that would influence the pattern of antibiotic prescription writing in a given population of prescribers and is cited along other factors that may contribute to any observed pattern of antibiotic prescribing as this study aims at establishing. For its investigation, a set of questions purposely designed to test prescribers' knowledge on the principles of antibiotic prescribing and the degree to which they apply such knowledge were included in the questionnaire (Questions 12 – 19). A marking scheme (Appendix 15) was prepared and used to assess the correctness of answers and scores of respondents.

Questions 13 and 17 in Part IV of the questionnaire were designed to test knowledge and additionally provide data that could be analysed to determine the extent to which respondents display good knowledge in their diagnosis and treatment of respiratory and urinary tract infections The questions specifically asked respondents to indicate signs and symptoms that lead to their diagnosis of bacterial infections of these anatomical sites (Question 13) as well as bacterial pathogens that are associated with infections at these sites (Question 17). The purpose of these questions was to provide data that could be analysed to establish extents to which respondents correctly diagnose and target the appropriate bacterial pathogens associated with respiratory and urinary tract infections, the two top ranking infections for which patients seek medical attention in Lesotho (Ministry of Health & Social Welfare, 2002:21, 32).

Part VI

Investigating major factors that prescribers consider when they select and prescribe a given antibiotic (Questions 20 – 22)

Questions in this part of the questionnaire were intended to investigate the degrees to which factors relating to antibiotics influence a respondent's selection of an antibiotic from a given list of antibiotics. Questions were structured to provide data that could be analysed to establish the extent to which antibiotic cost, pathogen sensitivity to antibiotics and antibiotic availability affects respondents' selection and prescription of their antibiotics of choice.

Part VII

Determining laboratory-related factors (Questions 23 – 25)

Questions in this part of the questionnaire have the purpose of

- assessing the efficiency of microbiology laboratories at study sites;
- determining the degree to which respondents use these facilities; and
- to investigating in cases of respondents' claim of a non-use of these facilities, what other specific reasons there may cite in explanation of such failures on the part of respondents to use these facilities.

Part VIII

Investigating opinions of prescribers on their needs for refresher courses and antibiotic prescription guidelines

For purposes of forming the basis of any recommendation that would propose the introduction of antibiotic treatment guidelines, this part of the questionnaire was designed to assess prescribers' need for antibiotic treatment guidelines or refresher courses on antibiotic use. Respondents were asked to express their opinions on whether or not they would find antibiotic treatment guidelines useful in their selection of antibiotics and also to grade their need for refresher courses on guiding principles of antibiotic prescribing.

♦ **Scaling of questionnaires**

Respondents' responses to questions meant to investigate prescribers' attitude in antibiotic prescription writing or their opinions on how they feel about issues pertaining to antibiotic prescribing were ranked generally on an ordinal type of scale that defined the degrees of their feelings or attitudes on a Likert attitude continuum scale (Aldridge & Levine, 2001:96; Bryman, 2004:68;). With the Likert scaling method respondents were asked to choose between three response categories that would indicate various strengths of their agreement or disagreement on an issue or their approval or disapproval of how a principle has been applied in antibiotic prescribing.

3.6.5 Questionnaire administration

The researcher distributed questionnaires to respondents directly and in person, instead of mailing them as also is permissible in questionnaire administration according to

Dawson (2006:89). A covering letter (Appendix 12) that explained the purpose of the study and which solicited the cooperation of respondents accompanied all questionnaires. Where requested to do so, the researcher explained questions that respondents otherwise claimed they did not perfectly understand. Completed questionnaires similarly were collected from respondents either directly or from study site pharmacies where respondents were asked to return them as a second option of returning completed questionnaires. The interaction of the researcher with respondents at the time of questionnaire distribution or their collection in the manner described and the fact that the researcher availed himself for an explanation of any question that was not properly understood by the respondent provided a questionnaire administration method that more closely resembles a combination of direct interview and self-administered questionnaire methods of data collection, except that the researcher in this case did not do any recording of respondents' response to any question.

3.6.6 Validation of data

Respondents' responses to questions were examined for purposes of validating and ensuring correctness of responses respondents provided to questions before data were analysed. This was done by comparing respondents' answers to questions that sought to know what they did particularly as they prescribed antibiotics in outpatient or inpatient settings with information they provided about their practice environments and patient types they saw. Responses to questions that linked what respondents did to what their practice environments dictated they do were, for example identified. Responses to such questions which were considered not being in conformity with the dictates of what respondents' practice environments would permit them to do were treated as errors. They were appropriately modified in all such cases to "not applicable", to indicate that such respondents should not have answered such questions.

3.6.7 Data analysis of Phase III

Frequency tables, pie charts and histograms where appropriate for descriptive statistical analysis were constructed and interpreted to establish the following:

- Questionnaire response rate and percentage distribution of respondents by their demographic data (Results: Table 4.3.1 and Figure 4.3.1 refer)

- Availabilities and capacities of microbiology laboratories at their prescribers' practice sites, patient types they see and their indications of daily patient workloads (Results: Tables 4.3.2 through and 4.3.7 refer)
- Degrees to which patient and prescriber related factors influence prescribers' decisions to prescribe antibiotics(Question 9), extent to which they prescribe antibiotics in outpatient departments only after establishing presence of infections (Question 10) and also extent to which they adhere to principles of rational prescribing of antibiotics in inpatient settings (Question 11) (Results: Tables 4.3.8 through 4.3.24 refer)
- Whether lack of adequate knowledge in general principles of antibiotic prescribing does exist among prescribers through assessment of prescribers' performance scores in test oriented questions that assessed their knowledge in the principles of rational antibiotic selection and prescribing (Questions 12 - 19) (Results: Tables 4.3.25 and 4.3.26 refer)
- Prescribers' ability to apply principles of antibiotic prescribing in practice based on knowledge of bacterial pathogen association with site and symptoms of infection (Questions 13 and 17) (Results: Tables 4.3.27 through 4.3.38 refer)
- Extent to which respondents of different qualifications comparatively display knowledge in their recognition of signs and symptoms and identification of bacterial pathogens associated with respiratory and urinary tract infections (Results: Table 4.3.39 refers).
- Extent to which factors of knowledge of morphological characteristics, antibiotic sensitivity and cost would influence prescribers' selection of antibiotics in practice (Questions 18,19 and 20) (Results: Tables 4.3.40 through 4.3.44 refer).
- Extent to which antibiotic unavailability in stock limits prescribers' ability to select antibiotics of choice (Questions 21 and 22) Tables 4.3.45 through 4.3.50 refer).
- Degrees to which prescribers use laboratory provided information on morphological characteristics of target bacterial pathogens as basis for empiric antibiotic prescribing (Questions 23, 24 and 25) (Results: Tables 4.3.51 through 4.3.53 refer).
- Extent of respondents need for antibiotic prescription guidelines and refresher courses in antibiotic prescribing (Questions 26 and 27) (Results: Tables 4.3.54 and 4.3.55 refer).

- **Establishing the extent to which prescribers prescribe antibiotics based on suspected or established presence of infections. (Question 10)**

Percentage frequencies of respondents' prescribing of antibiotics in practice based on suspected or established presence of infections were determined on the following assumptions and calculations:

- Responses of "ALWAYS" and "SOMETIMES" to questions that sought to establish the extent to which respondents prescribed antibiotics on suspicion of the presence of infections both indicate frequencies of antibiotic prescriptions being possibly written for this reason. The response of "SOMETIMES" to the question indicates an admission of a respondent to prescribing an antibiotic on the basis of presenting symptoms and hence assumed to indicate a probability of the respondent prescribing antibiotics on the basis of what the statement implies. Responses of "ALWAYS" and "SOMETIMES" were, for these assumptions, summed to indicate the total number of respondents most likely to prescribe antibiotics on suspicion of the presence of infections. It is permissible according to Neuman (2006:207) for a researcher to combine or collapse categories on Likert scales to make data more precise even after their collection.

Along this same principles the following responses to indicated questions were given their implied practical meanings and appropriately combined to make data more precise for analysis:

- Frequencies of "ALWAYS" and "SOMETIMES" as responses to questions that sought to establish the extent to which respondents prescribe antibiotics when they are not sure of their diagnosis, were summed up to determine total frequencies of respondents that would most likely prescribe antibiotics even if they were not sure of the presence of infections after a diagnostic workup.

- Prescribing antibiotics based on patients' presenting symptoms or prescribing antibiotics in the event of respondents not being sure of their diagnosis, all indicate situations in which respondents prescribe antibiotics without establishing the presence of infections.

- Physical examination of patients is considered a necessary step in diagnostic workups required to determine the diagnosis of a patient's complaints. A respondent indicating that he or she examined patients SOMETIMES only before deciding to prescribe antibiotics was taken as one who admits not to examining patients always as procedures require in the establishment of the presence of infections before antibiotics are prescribed. Responses of "SOMETIMES" and "NEVER" to question seeking to establish how often respondents would prescribe antibiotics only after patient examination were combined to denote total number of respondents who would most likely prescribe antibiotics without establishing presence of infections through physical examinations of patients.

- Laboratory investigation may be done to confirm or as part of initial diagnostic procedures to establish presence of infections and it may be performed only when a respondent finds the need to do so. Responses of "SOMETIMES" to the question of how often respondents prescribe antibiotics only after they positively had established presence of infections through laboratory investigations were interpreted for this reason to indicate respondents' inclination to confirming, or establishing the presence of infections, if necessary, before deciding to prescribe antibiotics. Responses of "ALWAYS" and "SOMETIMES" of respondents to the question were thus summed to denote category of respondents who were most inclined to prescribing antibiotics based on objective data as provided by results of laboratory investigations to establish or confirm the presence of infections.

- Contingency tables of percentage frequency distributions of respondents according to how often they prescribed antibiotics in practice in outpatient settings without establishing (Table 4.3.18a) or establishing (Table 4.3.18a) presence of infections were constructed and respectively analysed to determine percentage frequency of respondents that would prescribe antibiotics based on
  - suspected presence of infections as inferred from presenting signs and symptoms of treated cases [Question 10(i); Table 4.3.18a];
  - suspected presence of infections from inconclusive diagnostic workups [Question 10(iv);Table 4.3.18a];
  - their establishment of presence of infections as inferred from results of patient examination [Question 10(ii); Table 4.3.18b); and

- establishment of presence of infections as inferred from results of laboratory investigations [Question 10(iii); Table 4.3.18b).

° Probabilities (P) or chances of respondents prescribing antibiotics on the basis of suspected and established infections were determined according to probability laws (Utts & Heckard, 2007:246; Turner and Knighton, 1989:271) from probabilities of respondents prescribing antibiotics in the events of
  - suspected presence of infections as inferred from presenting signs and symptoms of treated cases [$P_{10(i)}$];
  - suspected presence of infections from inconclusive diagnostic workups [$P_{10(iv)}$];
  - established infections based on results of patient examination [$P_{10(ii)}$]; and
  - established infections based on results of laboratory investigations [$P_{10(iii)}$].

° Probability of antibiotics being prescribed without respondents establishing presence of infections [$P_{(PAWEPI)}$] by the above considerations was determined as the product of the probabilities of respondents prescribing the agents based on presenting signs and symptoms ($P_{(10i)}$) and results of inconclusive diagnosis ($P_{(10iv)}$). This is expressed as:

$$P_{(PAWEPI)} = [P_{(10i)}] \cap [P_{(10iv)}]$$

° Probability of antibiotics being prescribed based on presence of infection $P_{(PABPI)}$ was similarly determined as the product of the probabilities of respondents prescribing the agents based on findings on patient examination ($P_{(10ii)}$) and laboratory investigations ($P_{(10iii)}$). This is expressed as

$$P_{(PABPI)} = [P_{(10ii)}] \cap [P_{(10iii)}]$$

Results obtained were used to predict expected patterns of antibiotic prescribing in outpatient departments of study sites and compared with patterns of antibiotic prescription established by results of antibiotic assessment study carried out in study Phase 1.

- **Establishing extent to which principles of rational antibiotic prescribing were adhered to in prescribing antibiotics in inpatient departments (Question 11)**

- **Assumptions and calculations**

Overall percentage frequencies of respondents abiding to or violating principles of antibiotic prescribing in inpatient settings were determined using assumptions based on logical reasoning in what a prescriber may or may not do to constitute an adherence or violation of these principles. These are as stipulated below:

- To be deemed as prescribing antibiotics appropriately according to principles of antibiotic prescribing respondents must or must not perform all activities listed in favour of principles of appropriate antibiotic prescribing.
- Depending on the degree of absoluteness of an activity in determining the appropriateness of an antibiotic prescription, an activity listed in favour of or in violation of principles of appropriate prescribing of antibiotics, may or may not be considered an activity that needs to be necessarily performed or violated for an antibiotic to be considered appropriately or inappropriately prescribed.
- Where a respondent answered "AT TIMES" to indicate he or she did or did not perform a listed activity such a response will be interpreted as compliance or non-compliance to antibiotic prescribing principles depending on whether or not the listed activity needs to be necessarily performed or violated for an antibiotic to be considered appropriately or inappropriately prescribed.

On the basis of these and for generating appropriate frequency tables for determining overall percentage frequencies of respondents abiding to or violating principles of antibiotic prescribing in inpatient settings respondents' responses to their performance of listed activities were given the interpretations listed below:

- Requesting for rapid microscopic identification of pathogens before starting antibiotic treatment (Question 11.i) may not necessarily have to be performed before an appropriate antibiotic choice is made depending on the type of infection being treated (Archer & Polk 2005:797). Some types of bacterial pathogens are known to be commonly associated with infections at certain body sites and hence become natural target pathogens against which antibiotics are selected (Guglielmo, 2008:56-1). A respondent with good knowledge and

experience on type of bacterial pathogens associated with a given infection at a given site may or may not find the need to perform this activity when treating such infections. Respondents indicating "YES" or "AT TIMES" to performing this activity were thus considered abiding to principle in appropriate prescription of antibiotics while a "NO" response indicates a respondent's violation of the principle and hence his or her lesser tendency to prescribe antibiotics appropriately.

- Requesting for culture sensitivity tests (CSTs) before initiating empiric antibiotic therapy (Question 11.ii) and revising antibiotic treatment by replacing initially prescribed antibiotics for antibiotics to which organisms are sensitive (Question 11.iv) are activities that need to be necessarily performed for antibiotics to be deemed appropriately prescribed in accordance with antibiotic prescribing principles (Chambers 2001: 1146; Scottish Inifections Standards and Strategies Group, 2003:282). Requesting for culture sensitivity tests after initiating antibiotic treatment may result in the inability to grow cultures of certain bacterial pathogens which otherwise might be responsible for the infection being treated (Bronska *et al.*, 2006:137; Popa *et al.,* 2009:227). Certain clinical infections may present in ways that may not permit easy taking of specimens for CSTs before antibiotic therapy initiation. In such cases dependence on knowledge of pathogens commonly associated with such infections may be the only means of appropriate antibiotic selection in principle in treating such infections (Archer & Polk, 2005:797). A prescriber considering such cases may indicate when asked whether or not he or she sends specimens for CSTs before antibiotic therapy initiation may respond "AT TIMES" and still be considered a respondent disposed to keeping with this principle in antibiotic prescribing.
- Antibiotics to which infecting bacterial pathogens are insensitive need not be retained in a previously prescribed treatment regimen due to their therapeutic inefficacy. Based on these considerations, respondents indicating "YES" and "AT TIMES" to sending specimens to laboratories for CSTs before initiating antibiotic therapy or "YES" to revising initial antibiotic treatments by replacing them for antibiotics to which organisms are sensitive may be considered abiding to the two principles. Similarly respondents indicating "NO" to sending specimens to laboratories for CSTs before initiating antibiotic therapy or "NO" or "AT TIMES" to revising initial antibiotic treatments by replacing them with

antibiotics to which organisms are sensitive may be considered violating these principles and demonstrate inclination to inappropriately prescribing antibiotics.

- Requesting for CSTs only in the event of treatment failure (Question11.iii) and revising antibiotic treatment by adding antibiotics to which organisms are sensitive to initially prescribed antibiotics (Question 11.v) are activities that are not to be performed in accordance with principles of antibiotic prescribing. The Scottish Infections Standards and Strategies (SISS) Group in its "occasional communication" on good practice guidance for antibiotic prescribing in hospitals indicated the collection of microbiology specimens for culture sensitivity tests being done prior to initial antimicrobial administration and that such an activity should be appropriately documented in patients' case notes [Scottish Inifections Standards and Strategies Group, 2003:282].
- Requesting for culture sensitivity tests after antibiotic treatment failure may result in the failure to grow cultures of certain bacteria that might be responsible for an infection. In support of this statement, reference is made to Bronska *et al.* (2006:137) who reported that conventional microscopy as well as culture methods may fail to allow the diagnosis of invasive meningococcal disease because of early administration of antibiotics. Similarly in their review on urinary tract infections in the potential vertebroplastic patient, Popa *et al.* (2009:227) indicated that urine culture and sensitivity should be obtained before initiation of antibiotic treatment. Retaining antibiotics to which organisms are not sensitive offers no therapeutic advantage. Respondents indicating "NO" to performing these two activities were considered abiding to principles of antibiotic prescribing while those indicating "YES" or "AT TIMES" to performing them violate antibiotic prescribing principles and demonstrate inclination to prescribing antibiotics in inpatient settings inappropriately.

– Overall percentage frequency of respondents with laboratory facilities who comply to principles of antibiotic prescribing in inpatient settings was calculated using the relationship

  OPF = (N/NR) (100)

  where

  OPF is the overall percentage frequency of respondents' indications of compliance to principles of antibiotic prescribing in inpatient settings;

N is the total frequency of respondents who responded to performing listed activities in ways tantamount to complying to or violating principles of antibiotic prescribing in inpatient environments with laboratory facilities; and **NR** is the total number of respondents responding each time to performing listed activities in ways they indicated. The rationale of determining the value of N is as explained in the analysis of data for Question 10 above.

- In the opinion of the researcher respondents will be more willing to indicate what they do in keeping to principles as they prescribe antibiotics than if manners of their antibiotic prescribing violate indicated principles. It is assumed on this basis that respondents who refused to respond to questions on principles of prescribing antibiotics were most likely to be rather violators than observers of the principles. On this assumption, frequencies of respondents identified with "NO RESPONSE" answers to questions on principles of antibiotic prescribing were added to frequencies of those providing responses that depict violations of the indicated principles [Results: Table 4.3.23 refer].

- **Analysis of respondents' scores (Questions 12 – 19)**

Respondents' marks were grouped into 5 ranges which included mark ranges of 80% – 100%, 60% – 79%, 40% – 59%, 20% – 39% and 0% – 20%. Respondents with marks falling in the ranges of 80% – 100%, 60% – 79%, 40% – 59%, 20% – 39% and 0% – 20% were respectively classified as having very good, good, fair, poor and very poor knowledge in principles of rational antibiotic selection and prescribing. Respondents' percentage frequency distributions by these classifications were determined, so also were any possible associations between marks scored and

- respondents' qualification,
- respondents' years of working experience.

- **Assessing respondents' abilities to apply principles of appropriate antibiotic prescribing in practice**

Respondents' abilities to apply principles of appropriate antibiotic prescribing in practice were assessed using their performance scores in questions 13, 17, 18 and

19. These were based on basic knowledge required for appropriate prescription of antibiotics in the management of respiratory and urinary tract infections, the two documented top ranking infectious diseases in Lesotho. Analysis of questions was based on the percentage distributions of respondents according to their correct or incorrect indications of

- signs and symptoms suggesting these infections;
- bacterial pathogens that are targeted in the selection of antibiotics to be used in the treatment of these infections; and
- antibiotics to be used in treating infections of gram positive cocci and gram negative bacilli based on their spectrum of activity and cost considerations.

On the basis of the assumption that a respondent would only intentionally refuse to answer a knowledge test question if he or she does not know the answer to such a question, frequency of respondents incorrectly indicating either signs and symptoms suggesting presence of listed infections or antibiotics indicated for such infections were taken to include number of respondents who either wrongly answered or refused to respond to such knowledge test questions.

3.7 Statistical methodology

All statistical analyses were performed using Microsoft Excel® and Statistical Analysis Systems® SAS for Windows 9.1®

Correlation coefficients, effect sizes (d-values) were used to make statistical inferences on the following:

- Correlations between appropriateness of antibiotic prescribing and antibiotic treatment outcomes and costs.
- Correlations between diagnosed infections and days of hospitalisation,
- Correlations between numbers of antibiotics and treatment costs and outcome indicators.

♦ Statistical correlations between appropriateness of antibiotic prescribing and antibiotic treatment outcomes

A contingency table of patient recovery status by prescription categories was used to determine statistics of correlation between the two variables. Contingency, phi and Cramer's V coefficients between the two variables were determined and used

to establish correlations between appropriateness of antibiotic prescribing and antibiotic treatment outcomes. A coefficient of 0.5 or greater is indicative of a significant correlation between the two variables.

- **Statistical methods of determining effects of appropriate antibiotic prescribing on treatment response indicators**

Effect sizes were determined and used as descriptive statistics to evaluate the impact of appropriate antibiotic prescribing on antibiotic treatment costs, effects of diagnosed infection on days of hospitalisation and also effect of number of prescribed antibiotics on treatment outcomes. Specifically, "effect sizes" or "d-values"

- were calculated for differences between average costs of prescribed antibiotics per prescription or average total costs of antibiotic treatment and hospitalisation for patient groups receiving antibiotic treatment on prescription categories "A1 and A2", "A1 and B" or "A2 and B" to establish the impact of appropriateness of antibiotic prescribing on these variables.
- Effect sizes for differences between average number of days of hospitalisation for patient groups diagnosed and not diagnosed for given infections were also determined and interpreted to establish the possible impact of diagnosed infections on days of hospitalisation .
- Effect size for differences between means of numbers of antibiotics used in treating groups of patients who
  - improved and who did not improve;
  - improved and who died; and
  - did not improve and who died.

Effect sizes or "d-values" standardise the differences between averages by dividing by a standard deviation. They are calculated from the relationship

$$\textbf{Effect size (d-values)} = \mu_1 - \mu_2 / \sigma^*$$

where, and as defined within the context of this study,

μ_1 and μ_2 are the means of the measurable variables of interest for two patient groups being compared, and σ^* the higher of two standard deviations about the means for the two groups.

Effect sizes provide information about how strong a difference or effect is in the population (Utts & Heckard, 2007: 582). Quoting Cohen (1988), Utts and Hackard (2007:582) arbitrarily defined effect sizes of 0.2, 0.5, and 0.8 are as small, medium and large. These effect sizes as the authors further explained demonstrate differences between the true mean from the null mean value that are respectively not obvious without statistics (small), obvious to a careful observer (medium), and obvious to most to most observers (large) (Utts & Hackard, 2007:583). Statistically the measures, apart from their use in testing hypotheses about means, are employed usefully in comparing research results across studies or comparing results on the same study topic in a research (Utts & Heckard, 2007: 580, 583, 584).

3.8 Chapter Summary

The methodology employed in this study has been presented in details in this chapter. The three phase design of the study with procedures followed at each of these phases summarised in diagrammed conceptual frameworks, has essentially been highlighted in the presentations. In Chapter 4 which follows, results as obtained for all three phases of the study have been presented and discussed.

RESULTS AND DISCUSSIONS

The chapter presents results and discussions of the research according to the three phases in which it was designed, namely, an antibiotic prescription pattern study in inpatient and outpatient departments of study sites (Phase I), determining antibiotic sensitivity patterns of isolated bacterial pathogens at study sites (Phase II) and an investigation of factors influencing patterns of antibiotic prescribing as the results of the research have established (Phase III).

The presentation is done in a format in which results of each analytical step within a given step of the research work are presented as tables, figures, calculations, statistical inferences where appropriate and then comprehensively reported. The presented results are evaluated and discussed conceptually within provisions of literature-derived information where found necessary, from a perspective that attempted to provide meanings to results obtained. Evaluations of results and discussions thereof in most cases are preceded by introductory paragraphs that generally highlighted the theoretical background and the rationale of conceptual thoughts on which said result evaluations and discussions are based.

Terms used in the presentation of the results as well as definitions considered limited to what they imply within the context of this study have been listed and defined at the end of the chapter. These include **absolute bacterial infections, Basotho, blood infections, bone infections, bukana, central nervous system infections, days of hospitalisation, formulary antibiotics, gastrointestinal tract/abdominal infections, general practitioners, genitourinary tract infections, nurse clinicians, nursing assistants, physician specialists, possible bacterial infections, practice location, practice type, prescriber, qualification, rate, registered nurses, relative/percentage frequencies, respiratory tract infections, rural area, skin and soft tissue infections, surgical consultants, symptom complexes, urban area, workload.** Other terms used, but which have either been explained in paragraphs where they were first used or listed and explained in earlier chapters, have not, been repeated.

4.1 EMPIRICAL RESEARCH PHASE I: APPROPRIATENESS ASSESSMENT OF INPATIENT AND OUTPATIENT ANTIBIOTIC PRESCRIPTIONS

Empirical research Phase I basically involved evaluating inpatient and outpatient antibiotic prescriptions to establish degrees to which prescribers write such prescriptions appropriately based on principles of antibiotic prescribing. In absence of documentations on prescribers providing respective treatments in patients' case notes no differences were made between prescriber qualifications who wrote prescriptions studied in both inpatient and outpatient departments as data were collected. Nurses, however, do not prescribe medications for inpatients and all prescriptions emanating from inpatient departments were taken to be written by doctors. In the case of outpatients, data were collected from patients' "bukana's" just after they had consulted respective prescribers and presented their bukanas at study site pharmacies for the dispensing of their prescribed drugs and it was possible to differentiate between prescriptions coming from doctors and nurses to enable these notations to be made as data were collected.

A method of analysis based on the extent to which prescriptions studied conform to set criteria formulated from principles of antibiotic prescribing was designed and used. Prescriptions were further classified into different categories of appropriateness and analysed to determine the impact that appropriateness of antibiotic prescribing, based on principles, would have on different modalities of results of infection treatment. .Treatment outcomes, costs of antibiotic treatment and days of hospitalisation of patients treated for infections in respective patient groups, inpatients and outpatients were also included. Data collected on prescribed antibiotics were also analysed to establish patterns of antibiotic use in the treatment of various clinical infections. Results obtained are presented and discussed in the subsections that follow.

4.1.1 Assessment of inpatient antibiotic prescriptions

Inpatient antibiotic prescriptions assessed were 307 in total and were collected from all study site hospitals, namely Berea, Maluti, Motebang, Queen II and Scott hospitals. Many such prescriptions studied had been prescribed together with other drugs as well. For each prescription, data were collected only on prescribed antibiotics regardless of whether they were prescribed with other drugs or not. Considerations of whether or not antibiotic prescriptions were changed during course of therapy were given to

prescriptions in which antibiotics were substituted or changed for other antibiotics and not when antibiotic formulations were changed from parenteral to oral formulations during course of antibiotic therapy.

4.1.1.1 Prescription categorisation and determination of percentage frequency distribution of prescription categories by study sites and ward types

The section presents results of percentage distribution of prescriptions according to study sites and also of the assessment of prescriptions according to various categories of appropriateness as defined in Table 3.1 and exemplified in Appendix 5. Percentage frequency distributions of assessed prescriptions according to categories of appropriateness into which they were classified and of classified prescription categories according to their sites of origin were determined and summarised. Results were conceptually evaluated and discussed to establish patterns of antibiotic prescribing and what such patterns mean in essence to patient care in respect to the treatment of infections at study site hospitals. The method and procedures used in assessing prescriptions, according to the researcher's concept, were also discussed to bring into view their strengths and weaknesses for readers' critical assessment.

4.1.1.1.1 Results

- **Percentage distribution of prescriptions according to study sites**

Figure 4.1.1 shows percentage frequency distribution of prescriptions according to study sites. Three hundred and seven (307) prescriptions were in total assessed, for all five study sites. Of this total,10.0.% were classified for Berea hospital, 12.0% for Maluti hospital, 29.0% for Motebang hospital, 38.0% for Queen II hospital and 11% for Scott hospital.

- **Prescription categorisation**

All 307 inpatient prescriptions studied for their appropriateness were successfully assessed and classified into seven (7) prescription categories designated A1, A2, B, C, D, E and F as defined in Table 3.1 by procedures detailed in Chapter 3, Sections 3.3.3 and 3.3.4.

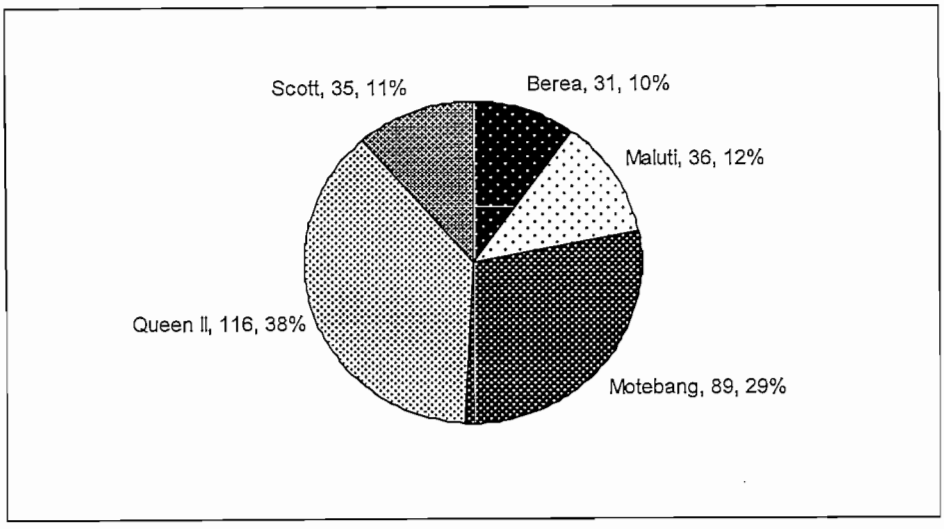

Figure 4.1.1 Percentage frequency distribution of prescriptions according to study sites

Respective percentage frequency distributions of prescriptions according to their classification categories, study sites and ward types from which they originated are shown in Tables 4.1.1, 4.1.2 and 4.1.3. Of the 307 inpatient antibiotic prescriptions assessed,

- 17.9% and 14.3%. were respectively prescriptions considered appropriately prescribed for the treatment of infections with absolute (prescription category A1) and possible (prescription Category A2) infections;
- 30.0% were prescriptions deemed inappropriately prescribed for the treatment of infections (prescription category B);
- category C prescriptions, constituted 1.3%. These were prescriptions of antibiotics which were prescribed according to results of culture sensitivity tests;
- 18.5% of the prescriptions were written for prevention of infections. They were respectively composed of 9.4% and 9.1% each of Category D and E prescriptions, which categories of prescriptions were considered prescribed appropriately and inappropriately for the prophylaxis of infection;

- prescriptions written for clinical conditions for which uses of antibiotics were considered not justified (prescription category F) totalled 17.9; and .
- 48.0% represented in total prescriptions that were inappropriately prescribed by set criteria considerations either for treatment of infections or for conditions in which the use of antibiotics unjustified.

Table 4.1.1 Percentage frequency distribution `of antibiotic prescriptions by categories according to total study sites. `

Antibiotic Prescription Category	Frequencies of prescription categories	
	n	n%
Prescription category A1	55	17.9
Prescription category A2	44	14.3
Subtotal (Appropriately prescribed)	**99**	**32.2**
Prescription category B	92	30
Prescription category F	55	17.9
Subtotal (Inappropriately prescribed)	**147**	**48**
Prescription category C	4	1.3
Subtotal(Prescribed on the basis of CST results	**4**	**1.3**
Prescription category D	29	9.4
Prescription category E	28	9.1
Subtotal (Prescribed for prophylaxis of infections)	**57**	**18.5**
TOTAL	**307**	**100**

- **Prescription category distribution by study sites**

Observed patterns of distribution of respective prescription categories were as follows.

- **Berea Hospital**:

  Of a total 31 prescriptions analysed for Berea hospital for their appropriateness,

  - 77.4% were prescribed for the treatment of infections;
  - 32.3% were prescribed appropriately for the treatment of infections with absolute (19.4% of prescription category A1) and possible (12.9% of prescription category A2) bacterial aetiologies;
  - 45. 2% were inappropriately prescribed for the treatment of (prescription category B);

- no antibiotic prescriptions from the study site were classified as category C;
- 6.5% made up of only prescription category D were prescribed for the prevention of infections; and
- total 16.1% were classified as category F.
- 61.3% were altogether prescribed inappropriately either for treatment of infections (category B prescriptions) or for clinical conditions for which antibiotics were regarded as not indicated (category F prescriptions).

- **Maluti Hospital**:

Total number of prescriptions assessed for their appropriateness for Maluti hospital was 36. Of this number,

- 66.7% made up of 27.8% of category A1, 13.9% of category A2 and 25.0% of category B prescriptions were prescribed for the treatment of infections;
- 41.7% were appropriately prescribed for treating absolute (prescription category A1) or possible (prescription category A2) bacterial infections;
- 25.0% were inappropriately prescribed for treatment of infections (prescription category B).
- No antibiotic prescriptions were classified as category C;
- 22.2% comprising 13.9% of category D and 8.3% of category E prescriptions were prescribed for the prophylaxis of infections;
- 11.1% were classified as prescription category F; and
- 36.1% were altogether prescribed inappropriately either for treatment of infections (category B prescriptions) or for clinical conditions for which antibiotics were deemed not indicated (category F prescriptions).

- **Motebang Hospital**:

Of a total 89 prescriptions assessed for the study site hospital for their appropriateness,

- 52.8% were prescribed for the treatment of infections;
- 29.2% were prescribed appropriately for the treatment of infections with absolute (prescription categories A1) or possible (prescription category A2) bacterial aetiologies;

- 23.6% were inappropriately prescribed for treating infections (prescription category B);
- no antibiotic prescriptions were classified in category C;
- 32.5% (29 out 89) comprising 11.2% and 21.3% of prescription categories D and E prescriptions were prescribed for the prevention of infections;
- 14.6% were prescribed for clinical conditions for which antibiotic prescriptions were considered not justified; and
- 38.2% were altogether inappropriately prescribed for the treatment of infections (prescription category B) or for clinical conditions considered not requiring antibiotics (prescription category F).

- **Queen II Hospital**:

Of a total 116 prescriptions assessed for the site hospital,

- 57.8%, comprising 13.8%, 11.2% and 32.8% of prescription categories A1, A2 and B were classified in the grouping of prescriptions given for treatment;
- 3.4% were classified as category C.
- 12.1% comprising respectively 9.5%) and 2.6% of prescription categories D and E were prescribed for the prevention of infections;
- 26.7% were classified as prescriptions given for clinical conditions for which use of antibiotics were considered unjustified (prescription category F); and
- 59.5% were in total prescribed inappropriately for treatment of infections (prescription category B) or for cases for which use of antibiotics were not justified (prescription category F).

- **Scott Hospital**

Of a total of 35 prescriptions assessed for their appropriateness for Scott hospital,

- 82.9%, composed of 20.1% of prescription category A1, 34.3% of prescription category A2 and 28.6% of prescription category B, were prescribed for the treatment of infections;
- No antibiotic prescriptions were classified as category C;
- 11.4% were prescribed for prevention of infections. They comprised 2.9% and 8.6% of prescription categories D and E;
- 5.7 were classified as prescription category F; and

- 34.3% were in total inappropriately prescribed for both treatment of infections and for cases not requiring antibiotic use (prescription categories B and F).

Table 4.1.2 Percentage frequency distribution of prescriptions by categories and according to study site hospitals

Prescription Categories	Frequency distribution of prescriptions according to defined prescription categories and study site hospitals										
	Berea		Maluti		Motebang		Queen II		Scott		Total
	n	n%	n	n%	n	n%	n	n%	n	n%	n
Category A1	6	19.4	10	27.8	16	18.0	16	13.8	7	20.1	55
Category A2	4	12.9	5	13.9	10	11.2	13	11.2	12	34.3	44
Category B	14	45.2	9	25.0	21	23.6	38	32.8	10	28.6	92
Subtotal (A1+A2 +B) (Empirically) Prescribed for the treatment of infections)	**24**	**77.4**	**24**	**66.7**	**47**	**52.8**	**67**	**57.8**	**29**	**82.9**	**191**
Category C	0	0.0	0	0.0	0	0.0	4	3.4	0	0.0	4
Subtotal (C) Prescribed on basis of CST results)	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**	**4**	**3.4**	**0**	**0.0**	**4**
Category D	2	6.5	5	13.9	10	11.2	11	9.5	1	2.9	29
Category E	0	0.0	3	8.3	19	21.3	3	2.6	3	8.6	28
Subtotal (D+E) Prescribed for the treatment of infections)	**2**	**6.5**	**8**	**22.2**	**29**	**32.5**	**14**	**12.1**	**4**	**11.4**	**57**
Category F	5	16.1	4	11.1	13	14.6	31	26.7	2	5.7	55
Subtotal (F) Prescribed for illnesses without bacterial aetiologies											
TOTAL	**31**	**100**	**36**	**100**	**89**	**100**	**116**	**100**	**35**	**100**	**307**

- **Comparative assessment of the extent of appropriate antibiotic prescribing at study sites**

Comparative prevalence of antibiotic prescribing at study site hospitals according to defined degrees of prescription appropriateness as further shown in Table 4.1.2 indicates that,

- antibiotics are prescribed appropriately for empiric treatment of absolute bacterial infections (prescription category A1) most prevalently in Maluti hospital

followed in that order by Scott hospital, Berea hospital, Motebang hospital and Queen II hospital;

- prescriptions appropriately given for empiric treatment of possible bacterial infections (prescription category A2), similarly, were most prevalent in Scott hospital and followed in that order by Maluti and Berea hospitals. Motebang and Queen II hospitals followed with a tie in rates at which prescribers prescribe antibiotics appropriately according to principles but for possible infections;
- antibiotics inappropriately prescribed for the empiric treatment of infections (prescription category B) are most prevalent in Berea hospital and followed in that order by Queen II, Scott, Maluti and Motebang hospitals;
- appropriate prescription of antibiotics for prevention of infections (prescription category D) is most prevalently done in Maluti hospital followed by Motebang, Queen II, Berea and Scott hospitals;
- inappropriate prescribing of antibiotics for the prevention of infections (prescription category E) is similarly most prevalent in Motebang hospital followed in that order by Scott hospital, Maluti hospital, Queen II hospital and Berea hospital;
- antibiotic prescribing for clinical conditions not needing antibiotic treatments is also observed to be most prevalently done at Queen II hospital followed respectively by Berea, Motebang, Maluti and Scott hospitals; and
- antibiotic prescribing based on laboratory investigations is more prevalently done at the Queen II hospital than any of the other study site hospitals;

- **Prescription category distribution by ward types**

Percentage frequency distributions of prescription categories according to types of wards from which they originate are shown in Table 4.1.3. Of the total number of antibiotic prescriptions assessed for all study sites (n = 307), 61.9% originated from medical wards and 38.1% from surgical wards. Percentage frequency distribution of respective prescription categories within the two ward types are indicated below:

- **Medical ward:**
  - A total 77.4% of assessed prescriptions were classified as A1, A2 and B in the grouping of antibiotic prescription given for the treatment of infections. Category

B prescriptions of this total represented 33.7% and categories A2 and A1, 22.6% and 21.1% of all prescriptions assessed for the ward type.

- Prescriptions considered in the category of antibiotic prescriptions written appropriately for the treatment of infections with absolute or possible bacterial aetiologies (prescription categories A1 and A2) totalled 43.7% of all prescriptions assessed for the ward type.
- No prescriptions were classified as category C for the ward type.
- Prescriptions classified in the grouping of antibiotic prescriptions given for prophylaxis of infections and which comprised only two prescriptions classified in category E represented 2.1% of total assessed prescriptions.
- Prescriptions given for the treatment of clinical conditions for which antibiotic use was considered not justified represented 20.5% of all prescriptions assessed for the ward type.
- Prescriptions considered in the grouping of antibiotic prescriptions inappropriately written either for the treatment of infections (prescription category B) or for clinical conditions not requiring antibiotic use (prescription category F) together represented 54.2%.
- Ratio of percentage frequencies of appropriately to inappropriately prescribed antibiotics was found to be 0.81.

- **Surgical ward**
  - Of the total number of antibiotic prescriptions assessed for surgical wards, 37.6% were classified as A1, A2 and B in the category of prescriptions given for the treatment of infections. Category B prescriptions of this total represented 23.9%, category A1 12.8% and category A2 0.9% of total prescriptions assessed for the ward type.
  - Prescriptions considered appropriately written by set criteria for the treatment of absolute or possible bacterial infections represented altogether 13.7% of total prescriptions assessed for the ward type.
  - Prescriptions classified in category C constituted 3.4% of total prescriptions assessed for the ward type.
  - In the grouping of antibiotic prescriptions given for the prophylaxis of infections 45.3% of total prescriptions assessed for the ward type and which comprised

24.8% and 20.5% of prescription categories D and E respectively, were classified.

- Prescriptions given for clinical conditions considered not requiring the use of antibiotics and classified in prescription category F represented 13.7% of assessed prescriptions for the ward type.
- Prescriptions inappropriately written either for the treatment of infections (prescription category B) or for clinical conditions not requiring antibiotic use (prescription category F) together represent 37.6% of total prescriptions assessed for the ward type.
- Ratio of percentage frequencies of appropriately to inappropriately prescribed antibiotics was determined as 0.36.

Percentage frequency distribution of prescription categories according to ward types as shown in Figure 4.1.2 indicates that:

- prescription categories A1, A2, B, and F, i.e. prescriptions classified in category groupings of antibiotic prescriptions given in the treatment of infections or suspected infections, being classified in medical wards at higher relative frequencies of 72.7%, 97.7%, 69.6% and 70.9% than they were in surgical wards where they were classified at low frequencies of 27.3%, 2.3%, 33.6% and 29.1%;
- all four (4) antibiotic prescriptions given on the basis of culture sensitivity results specifically were seen in surgical and not medical wards; and
- all prescriptions classified as category D and 87.5% of those classified as category E were seen in surgical wards. In other words prescriptions classified in category groupings of antibiotic prescriptions given for prophylaxis of infections were seen at much higher frequencies in surgical than medical wards.

Table 4.1.3 Percentage frequency distribution of prescription categories by ward types

Ward type	Frequencies of prescription categories																Ratio of % frequencies of appropriately to inappropriately written prescriptions
	Prescription category A1		Prescription category A2		Prescription category B		Prescription category C		Prescription category D		Prescription category E		Prescription category F		Total		
	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	
Medical	40	72.7 (21.1)	43	97.7 (22.6)	64	69.6 (33.7)	0	0.0 (0.0)	0	0.0 (0.0)	4	14.3 (2.1)	39	70.9 (20.5)	190	61.9 (100)	0.81
Surgical	15	27.3 (12.8)	1	2.3 (0.9)	28	30.4 (23.9)	4	100 (3.4)	29	100 (24.8)	24	85.7 (20.5)	16	29.1 (13.7)	117	38.1 (100)	0.36
Total	55	100	44	100	92	100	4	100	29	100	28	100	55	100	307	100	

Notations: n% value in bracket determinations based on row totals
n% value not in bracket determinations based on column totals

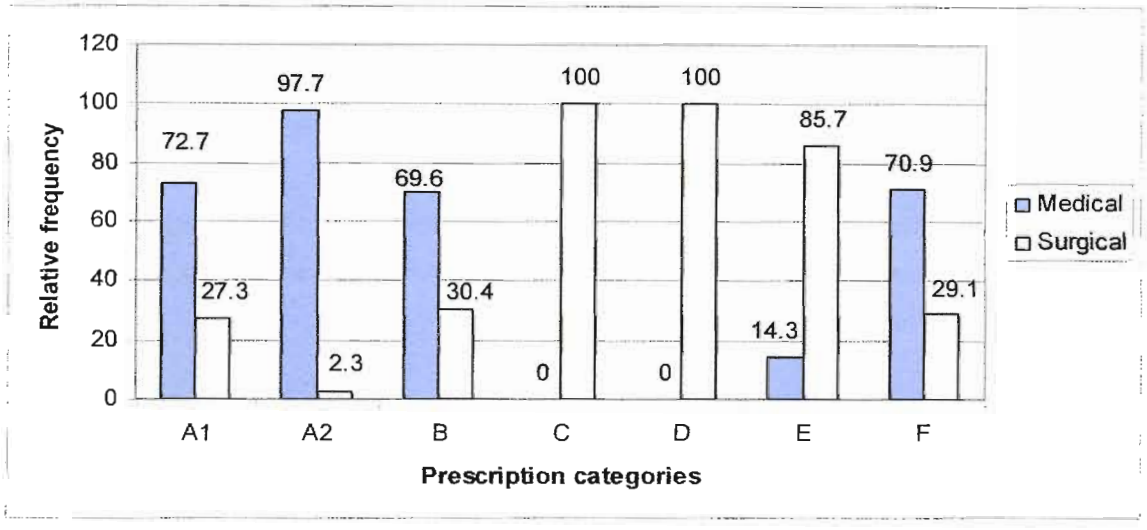

Figure 4.1.2 Percentage frequency distribution of prescription categories according to ward types

4.1.1.1.2 Results evaluation and discussion

- **Methodology of prescription assessment**

Difficulties of assessing antibiotic prescriptions and the merits and demerits of methods used by various researchers in assessing these prescriptions are reviewed in Section 2.6.

The methodology of assessing the appropriateness of antibiotic prescriptions employed an instrument which was developed based on prescribers' adherence to principles of antibiotic prescribing (Chapter 3, Sections 3.2.1 and 3.2.3) as documented in literature reviewed for the purpose. It provides a novel approach to the assessment of antibiotic prescriptions that avoided the use of experts in infectious disease management in prescription assessment procedures entailed in studies of this kind or the use of treatment guidelines as reference points of assessing appropriateness of antibiotic prescriptions as reported in the literature (Akkerman *et al.*, 2005:570). As indicated in

Section 2.6, in clinical environments where neither infectious disease experts nor types of antibiotic treatment guidelines that could be used reliably in antibiotic prescription assessment studies are available, it is impossible to use such means in assessing the appropriateness of antibiotic prescriptions. These two situations prevail in Lesotho, and it is therefore impossible services of infectious disease experts or even information from national treatment guidelines in developing procedures for assessing antibiotic prescriptions in studies of the kind being undertaken in this research. Assessing antibiotic prescriptions based on prescribers' adherence to antibiotic prescribing principles also provides a means of generally evaluating antibiotic prescriptions from broader perspectives including the establishment of the need of antibiotics, among other things, before the agents are prescribed.

In its general design a layout of the Akkerman *et al.* (2005:570) method that did not use experts in the development of instruments for the assessment of prescriptions in their study (Section 2.6) was adopted. This was done with a modification that included the use of literature-derived information in designing an instrument for assessing the appropriateness of antibiotic prescriptions. Britten *et al.* (2003:246) similarly used literature-derived information in developing the medication appropriateness index (MAI) which is used as an instrument in assessing the appropriateness of prescriptions. The method generally assessed antibiotic prescriptions against the establishment of the need for antibiotic use in circumstances for which the prescriptions were made. It also assessed the appropriate prescribing of antibiotics with respect to their doses, compatibility with co-prescribed antibiotics and effectiveness of the prescribed drugs against pathogens commonly implicated in infections for which they have been prescribed. It fundamentally employed the basic principle that antibiotics prescribed in accordance with principles, would generate antibiotic prescriptions with appropriately prescribed antibiotics to ensure effective treatment of infections at minimum costs to patients and health institutions.

The use of criteria developed from principles of antibiotic prescribing as an instrument in assessing antibiotic prescriptions is considered a strength of the method. It enabled the classification of antibiotic prescriptions not only into categories of appropriately and inappropriately written prescriptions but also enabled antibiotic prescriptions to be classified into different categories of appropriateness according to reasons why they

were so classified irrespective of whether or not they were written appropriately according to principles. This made it possible to identify problem areas of antibiotic prescribing and the reasons contributing to such problems. Knowing such reasons, particularly those explaining the extent to which antibiotic prescriptions are written inappropriately, facilitates the formulation of policies necessary to promote the rational prescribing and use of these drugs.

The greatest challenge of the use of the method and which is considered a limitation in accurate assessment of prescriptions is the ability of a researcher using the method to correctly decide whether or not a prescription being assessed conforms to set criteria against which it is evaluated. Inability to correctly decide on the conformity of a prescription to such set criteria compromises results. To address this challenge, informed decisions on the conformity of prescriptions to the assessment criteria, were made based on contents of data collection tools that provided literature-derived information on infections and their causative agents as well as the therapeutic and physico-chemical properties of antibiotics for reference in the prescription assessment procedure where needed (Appendixes 5 and 6).

- **Prescription assessment results**

Results emanating from assessment of inpatient prescriptions from different study site hospitals revealed high prevalence of inappropriate prescribing of antibiotics in the country's hospitals both for treatment and prophylaxis of infections and raised curtains on problems of antibiotic use in the country. Such problems are to be addressed in the interest of cost-effective management of infections. This is shown by an overall 57.0% of total assessed prescriptions being found to be prescriptions classified as categories B, E and F (Table 4.1.2). These, by definition, are prescriptions inappropriately written for treatment or prophylaxis of infections or for clinical conditions considered not requiring use of antibiotics in their management. By comparison a lower proportion of 42.9% (n = 132) of total prescriptions assessed were classified as appropriately prescribed for either treatment or prophylaxis of infections in prescription categories A1, A2, C and D (Table 4.1.2). Prescriptions classified in category F represent 17.9% of total inpatient prescriptions assessed and constitute the category of prescriptions in which prescribed antibiotics were considered wasted on account of their being unjustifiably prescribed in the treatment of clinical conditions for which bacterial infections are not aetiologies. In

monetary terms this translates into a calculated loss of about R7858.15, being the cost of prescribed antibiotics on these types of inpatient antibiotic prescriptions as classified for the five study site hospitals during the one-month study period (Table 4.1.10).

The trend of inappropriate prescribing of antibiotics for inpatients comparatively is more associated with government than the Christian Hospitals Association of Lesotho (CHAL) hospitals (Table 4.1.2). Results of the assessment showed higher tendencies of antibiotics being appropriately prescribed in the latter hospital types than in the former. This is shown by the respective calculated average rates of prescribing antibiotics appropriately for absolute bacterial infections (prescription categories A1) and possible bacterial infections (prescription categories A2) which are 24.0% and 24.1% by prescribers of CHAL and 17.0% and 11.7% by prescribers of government hospitals (Table 4.1.2). Further indicating a trend of inappropriate prescribing of antibiotics for inpatients being associated more with government than CHAL hospitals, average rates of prescribing antibiotics inappropriately for the treatment of infections or for conditions not needing antibiotic treatments were again observed to be higher for government hospitals (53.0%) than for CHAL hospitals (35.2%) (Table 4.1.2). It is difficult to explain this observed trend in antibiotic prescribing in the two types of hospitals based on any of the findings from this research. Being self-financing hospitals that undoubtedly operate with independent internal policies with orientations towards operational cost recovery, it is highly possible that these hospitals operate with stricter regulations in the use of antibiotics that in the long run tend to promote more judicious and expedient use of the class of drugs. It is noted here in accordance with results of outpatient prescription analysis (Results: 4.1.2.3.1) that availability of antibiotics was not shown as a factor that affects prescribers' choices of antibiotics and hence the appropriateness of antibiotic prescribing in either of the two types of study site hospitals.

- **Patterns of antibiotic prescribing in medical and surgical wards**

Only 2.1% of total antibiotic prescriptions assessed for medical wards were given for the prophylaxis of infections as opposed to surgical wards where as many as 45.3% of prescriptions assessed were seen to be given for prevention of infections. These observed trends in antibiotic prescribing for inpatients established patterns in which antibiotics are seen to be prescribed mainly for the treatment of infections in medical wards but almost equally for treatment and prophylaxis of infections in surgical wards.

This is an expected pattern of antibiotic prescribing in the two ward types, considering that the majority of patients treated with antibiotics in medical wards are admitted in the first instance for medical problems with bacterial infections as aetiologies. In surgical wards where surgical incisions have the potential of introducing bacteria inoculums into tissues with possible resultant bacterial colonisation and infection, the natural tendency in antibiotic prescribing would be to prevent such bacterial colonisation in surgical wounds from developing into infections or to treat such infections in the event of their occurrence.

From results of appropriateness assessment of prescriptions, 3.4% only of prescriptions emanating from surgical wards and none from medical wards were classified in category C. It can be inferred from this that antibiotic prescribing based on results of culture sensitivity tests is not an important feature of patterns of antibiotic prescribing at study site hospitals. This finding has in other words established empiric antibiotic prescribing as a mainstay of infection treatment at study site hospitals, even within inpatient settings of these hospitals. The deliberate choice of study sites to include Lesotho's biggest hospitals and also produce total hospital bed capacity of 2468, equivalent to almost 50% of bed capacities of all hospitals in Lesotho (Ministry of Health and Social Welfare Lesotho, 2002: 4), allows this conclusion to be extended to depict the country situation. The finding gives reason for concern because of results of Phase II of the study which reported high levels of resistance to antibiotics most commonly prescribed. Empiric antibiotic prescribing being established as the mainstay of antibiotic treatment in the country, even among inpatients as observed, raises the question of how effectively patients are treated for infections when interpreted in conjunction with the reported results of study Phase II as mentioned above. Considered as raising a curtain on a problem that may have been compromising infection treatment outcomes, this question is relevant and merit attention. Recommendations to this effect have been made in Section 5.7.

Also shown as a characteristic pattern of antibiotic prescribing for inpatients at the study hospitals, is the higher percentage of appropriately written prescriptions in surgical wards being prescriptions for clinical conditions in which bacterial pathogens were absolute than being possible aetiologies. This is inferred from results of the prescription assessment that gave 2.3% of total prescriptions assessed for surgical wards as

belonging to prescription category A2 as against a reported 27.3% for A1 category of prescriptions (Figure 4.1.2). One would have expected on this account a more precise targeting of infecting organisms and hence a more expedient prescribing of antibiotics that would reflect in results obtained showing percentage of total prescriptions classified as A1 and A2 (appropriately prescribed) being higher than percentage of total prescriptions classified as B and F (inappropriately prescribed) in surgical wards. Contrary to this, a higher percentage of prescriptions inappropriately prescribed for treatment of infections was determined as 37.6% (total percentages of categories B and F prescriptions) as against a 13.7% determined as percentage totals of categories A1 and A2 prescriptions in surgical wards. The total percentages of categories A1 and A2 prescriptions on one hand and categories B and F prescriptions on the other are respectively 43.7% and 54.2% for medical wards. The higher percentage totals of inappropriately written in comparison appropriately written prescriptions in both medical and surgical wards indicate a high prevalence of inappropriate prescribing of antibiotics in the two types of wards. The observation is further confirmed by the determined ratios of percentage frequencies of appropriately to inappropriately written prescriptions for surgical and medical wards which were respectively shown as 0.36 and 0.81 for the two wards. That these ratios are below1 (one) indicates a high prevalence of inappropriate prescribing of antibiotics in the two ward types. By comparison of the two ratios, inappropriate prescribing of antibiotics for infection treatment is seen to prevail more in surgical than medical wards.

4.1.1.2 Determining the impact of appropriate or inappropriate prescribing of antibiotics on treatment outcomes, days of hospitalisation, and costs of treatment.

Results presented in this section show findings of the assessment of inpatient prescriptions with respect to outcomes that were seen to be associated with categories of appropriateness of antibiotic prescriptions as results of the study had established. Three outcomes, inclusive of the end points of antibiotic treatment offered patients, the number of days patients spent in hospital on admission for infections and the costs of treating such infections with antibiotics were selected and investigated for the impact appropriate and inappropriate prescribing of antibiotics, based on prescribers' adherence to principles of antibiotic prescribing, would have on them Tabular analysis of data

supported where necessary by statistical inferences, has mainly been used in these investigations. Results obtained are shown in paragraphs that follow.

4.1.1.2.1 Results

- **Impact of appropriateness of antibiotic prescribing on treatment outcomes**

Tables 4.1.4.1 through to Table 4.1.4.4 show percentage frequency distributions of prescriptions in various classification categories according to patient treatment outcome indicators defined as "improved", "not improved" or "died". Table 4.1.5 on the other hand shows percentage frequency distributions of antibiotic treatment response indicators as well as calculated therapeutic success rates for patient groups given antibiotic prescriptions classified in respective prescription categories.

- **Frequency distributions of prescription categories**

  Result presentations in Tables 4.1.4.1 to 4.1.4.4 show the following,

  - Of a total of 55 patients who received antibiotics on prescriptions classified in category A1, 72.8% improved as against 13.0% in each case who did not improve and who died.
  - Of a total of 44 patients who received antibiotics on prescriptions classified in category A2, 61.4% improved as against 22.8% who did not improve and 22.3% who died.
  - Of a total of 99 patients who received antibiotics on prescriptions classified as appropriately prescribed, that is prescription categories A1 and A2, 67.7% improved as against 14.1% who did not improve and 17.2% who died.
  - Of a total of 92 patients who received antibiotics on prescriptions classified in category B, 63.0% improved as against 21.0% who did not improve and 14.1% who died.
  - All four (4) patients treated with antibiotics on prescriptions classified in category C improved.

Table 4.1.4.1 Percentage frequency distribution of CATEGORY A1 PRESCRIPTIONS by treatment outcomes and according to study sites

Study site	Prescription frequencies by patient treatment outcomes						
	Improved		Not improved		Died		Total
	n	n%	n	n%	n	n%	n
Berea	3	50	0	0.0	2	33.3	6
Maluti	10	100	0	0.0	0	0.0	10
Motebang	11	68.8	4	25.0	1	6.3	16
Queen II	12	75	1	6.3	3	18.8	16
Scott	4	57.1	2	28.6	1	14.3	7
Total	40	72.8	7	13	7	13	55

Table 4.1.4 .2 Percentage frequency distribution of CATEGORY A2 PRESCRIPTIONS by treatment outcomes and according to study sites

Study site	Prescription frequencies by patient treatment outcomes						
	Improved		Not improved		Died		Total
	n	n%	n	n%	n	n%	n
Berea	2	50.0	2	50.0	0	0.0	4
Maluti	5	100	0	0.0	0	0.0	5
Motebang	5	50.0	3	30.0	2	20.0	10
Queen II	7	53.8	1	76.9	5	38.5	13
Scott	8	66.7	1	8.3	3	25.0	12
Total	27	61.4	7	15.9	10	22.3	44

Table 4.1.4 .3 Percentage frequency distribution of CATEGORY B PRESCRIPTIONS by treatment outcomes and according to study sites

Study site	Prescription frequencies by patient treatment outcomes						
	Improved		Not improved		Died		Total
	n	n%	n	n%	n	n%	n
Berea	9	64.2	3	21.4	2	14.3	14
Maluti	9	100	0	0.0	0	0.0	9
Motebang	14	47.6	5	23.8	2	9.5	21
Queen II	22	57.8	9	23.7	7	18.4	38
Scott	4	40.0	4	40	2	20	10
Total	58	63.0	21	22.8	13	14.1	92

Table 4.1.4 .4: Percentage frequency distribution of CATEGORY C PRESCRIPTIONS by treatment outcomes and according to study sites

Study site	Prescription frequencies by patient treatment outcomes						
	Improved		Not improved		Died		Total
	n	n%	n	n%	n	n%	0
Berea	0	0.0	0	0.0	0	0.0	0
Maluti	0	0.0	0	0.0	0	0.0	0
Motebang	0	0.0	0	0.0	0	0.0	0
Queen II	4	100	0	0.0	0	0.0	4
Scott	0	0.0	0	0.0	0	0.0	0
Total	4	100	0	0.0	0	0.0	4

Notation: n% value determinations (Tables 4.1.4.1 through 4.1.4.4) based on row totals

- **Treatment success rate (TSR) determinations**

  Antibiotic treatment success rates for patient groups receiving antibiotic treatment on respective prescription categories were determined as ranges of calculated TSRs based on total number of patients receiving antibiotic prescriptions for treatments of various infections from all study sites that included and excluded patients who died in the course of treatment. Deaths of patients, for reasons given in Section 3.2.1, cannot be absolutely attributed to non-response of patients to antibiotics used in treating their infections. By result indications in Table 4.1.5 the following are documented as determined treatment success rates of patient groups receiving antibiotics prescribed on various prescription categories.

  - Treatment success rate for all patients receiving antibiotic treatment irrespective of prescription category type was determined as (67.2 - 78.9)%
  - Treatment success rates for patient groups treated with antibiotic prescriptions classified as A1, A2, B and C were determined as
    - 74.5% -85.4% for prescription category A1
    - 61.4% - 79.4% for prescription category A2
    - 64.1% - 73.8% for prescription category B and
    - 100% for prescription category C
  - Corresponding relative treatment success rates for patient groups treated with respective antibiotic prescription categories were
    - 1.09 for prescription category A1
    - 0.96 for prescription category A2
    - 0.95 for prescription category B and
    - 1.26 for prescription category C

- **Statistical correlations: Percentage frequencies of prescription by their appropriateness categories versus recovery status**

  - Contingency, phi and Cramer's V coefficients which defined the relationship between appropriateness of antibiotic prescribing as determined by prescription categories and recovery status were 0.1902 0.1938 and 0.1370

- **Impact of appropriateness of antibiotic prescribing on days of patients' hospitalisation.**

Percentage frequencies of numbers of days patients spent in hospital according to categories of antibiotic prescriptions are shown in Table 4.1.6 and summarised as shown below.

- Average number of days of hospitalisation for patients receiving antibiotic treatment on prescriptions classified as categories A1 and A2 were 8.7±7.3 and 7.4±7.6 respectively, giving 8.1 days as average number of days spent in hospital by patients treated with antibiotics deemed appropriately prescribed.
- Patients treated with antibiotics prescribed on the basis of culture sensitivity test results (prescription category C) were found to spend an average of 36.6 ±15.6 days on hospital admission.
- Maximum numbers of days spent by patients treated with antibiotics on prescriptions classified in the respective prescription categories were 38 for prescription category A1, 49 for A2, 74 for B and 59 for C.

- **Impact of diagnosed infections on days of patients' hospitalisation.**

Percentage frequencies of prescription categories according to diagnoses for which they were prescribed are shown in Table 4.1.7. Effect sizes for differences between means of days of hospitalisation for patient groups diagnosed and not diagnosed for given infections are also shown in Table 4.1.8. Table 4.1.9 shows percentage frequencies and mean days of hospitalisation of patients treated with antibiotic prescription categories A1, A2 and B for diagnosed infections as summarised from Tables 4.1.6.2 and 4.1.6.3. Results as indicated in these tables are outlined as follows:

Table 4.1.5 Percentage frequencies of antibiotic treatment response indicators and calculated therapeutic success rates by prescription categories

Prescription category	Number of patients (Deaths excluded)	Frequencies of Treatment Response						Number of patients (Deaths excluded)	Category Treatment success rates ($TSR_{(cat)}$			Category relative treatment success rate (stated as range and average)
		Improved (I)		Not improved (NI)		Died			Deaths inclusive (%)	Deaths exclusive (%)	Range (%)	
	n	n	n%	n	n%	n	n%	n				
Category A1	55	41	74.5	7	12.7	7	12.7	48	74.5	85.4	74.5-85.4	1.1-1.08 (1.09)
Category A2	44	27	61.4	7	15.9	10	22.7	34	61.4	79.4	61.4-79.4	0.91-1.0 (0.96)
Category B	92	59	64.1	21	22.8	12	13.0	80	64.1	73.8	64.1-73.8	0.95-0.94(0.95)
Category C	4	4	100	0	0.0	0	0.0	4	100	100	---	1.26
Total	195	131	67.2	35	17.9	29	14.9	166	—	—	—	—

Treatment success rate (including deaths) (All categories) (%): 67.2
Treatment success rate (excluding deaths) (All categories) (%): 78.9
Treatment success rate (All categories) (%): 67.2 - 78.9

Table 4.1.6 Percentage frequencies of number of days patients were in hospital according to prescription categories

Prescription categories	Number of prescriptions in category	Number of days of spent in hospital			
		Minimum number of days spent at hospital	Maximum number of days spent at hospital	Mean or Average number of days of hospitalisation	Standard deviation
Prescription category A1	55	1.0	38	8.7 ±7.3	±7.3
Prescription category A2	44	1.0	49	7.4 ±7.6	±7.6
Prescription category B	92	1.0	74	13.8 ±14.8	±14.8
Prescription Category C (Patient category receiving antibiotics prescribed based on culture sensitivity results	4	25	59	36 ±15.6	±15.6

Table 4.1.7 Frequencies of prescription categories according to diagnoses for which they were prescribed

Diagnosis	Frequencies of prescription categories															
	Prescription category A1		Prescription category A2		Prescription category B		Prescription category C		Prescription category D		Prescription category E		Prescription category F		Total	
	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
Respiratory tract infections	28	42.4 (26.9)	26	47.2 (25.0)	40	36.0 (38.5)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	10	11.4 (9.6)	104	27.1 (100)
Gastrointestinal infections	6	9.1 (14.3)	16	29.1 (38.1)	13	11,7 (31.0)	1	25.0 (2.4)	5	15.6 (11.9)	0	0.0 (0.0)	1	1.1 (2,4)	42	10.9 (100)
Genitourinary tract infections	12	18.2 (33.3)	1	1.8 (2.7)	13	11.7 (36.1)	0	0.0 (0.0)	4	12.5 (11.1)	2	7.1 (5.6)	4	4.5 (11.1)	36	9.4 (100)
Skin and soft tissue infections	14	21.2 (15.9)	2	3.6 (2.3)	26	23.4 (29.5)	3	75.0 (3.4)	19	59.4 (21.6)	23	82.1 (26.1)	1	1.1 (1.1)	88	22.9 (100)
Bone infections	2	3.0 (28.6)	0	0.0 (0.0)	3	2.7 (42.9)	0	0.0 (0.0)	1	3.1 (14.3)	1	3.6 (14.3)	0	0.0 (0.0)	7	1.8 (100)
Central nervous system infect.	0	0.0 (0.0)	1	1.8 (8.3)	9	8.1 (75.0)	0	0.0 (0.0)	0	0.0 (0.0)	1	3.6 (8.3)	1	1.1 (8.3)	12	3.1 (100)
Blood infections	3	4.5 (100)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	3	0.8 (100)
Fevers of unknown origin	1	1.5 (5.9)	9	16.4 (52.9)	7	6.3 (41.2)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	17	4.4 (100)
Non infectious diseases	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	3	(9.4) (4.0)	1	3.6 (1.3)	71	80.7 (94.7)	75	19.5 (100)
Total	66	100	55	100	111	100	4	100	32	100	28	100	88	100	384*	100

Notation: n% values in bracket are based on row totals
n% values not in bracket based on column totals

*The total number of times (384) prescription categories were prescribed for infections was seen to be greater than the total number of 307 records analysed. This is a result of instances where some patients were diagnosed with more than one infection but got treated with given prescription categories they were prescribed. In such instances, the given prescription categories in terms of counts were used for a number of times equivalent to the number of infections diagnosed in those patients.

Table 4.1.8 Effect sizes for differences between means of number of days of hospitalisation for patient groups diagnosed and not diagnosed for given infections (excluding deaths).

Diagnosis	Patient groups	Number of patients in group	Days of hospitalisation			Statistics	
			Minimum	Maximum	Mean	Standard deviation	Effect size (d)
Respiratory tract infection	Diagnosed	93	1	19	8.06	4.49	0.40
	Not Diagnosed	99	1	74	14.51	16.04	
Gastrointestinal infection	Diagnosed	36	1	30	6.50	5.73	0.46
	Not Diagnosed	156	1	74	12.51	13.16	
Genitourinary tract infection	Diagnosed	25	2	60	13.20	15.20	- 0.14
	Not Diagnosed	167	1	74	11.11	11.88	
Skin and soft tissue infection	Diagnosed	44	2	74	21.64	18.63	- 0.71
	Not Diagnosed	148	1	58	8.34	7.45	
Bone infections	Diagnosed	5	4	51	22.40	18.69	- 0.61
	Not Diagnosed	187	1	74	11.09	12.06	
Central nervous system infections	Diagnosed	10	1	18	8.40	4.53	0.25
	Not Diagnosed	182	1	74	11.55	12.61	
Blood infections	Diagnosed	3	2	9	4.33	4.04	0.58
	Not Diagnosed	189	1	74	11.50	12.39	
Fevers of unknown origin	Diagnosed	17	3	49	12.12	10.70	- 0.06
	Not Diagnosed	175	1	74	11.31	12.51	
Non infectious diseases	Diagnosed	24	4	49	10.25	9.34	0.01
	Not Diagnosed	167	1	74	11.56	12.76	

Table 4.1.9 Percentage frequencies and mean days of hospitalisation of patients treated with antibiotic prescription categories A1, A2 and B for diagnosed infections.

Prescription category use in treating patient group	Average number of days of hospitalisation	Percentage frequencies of patients treated							
		RTI	SSI	GITI	GUTI	BI	CNSI	BLDI	FUO
		% F	% F	% F	% F	% F	% F	% F	% F
Prescription category A1	8.7 ±7.3	26.9	15.9	14.3	33.3	28.6	0.0	100	5.9
Prescription category A2	7.4 ±7.6	25.0	2.3	38.1	2.7	0.0	8.3	0.0	52.9
Prescription category B	13.8 ±14.8	38.5	29.5	31.0	36.1	42.9	75.0	0.0	41.2

Abbreviations:

RTI;	Respiratory tract infections
SSI:	Skin and soft tissue infections
GITI;	Gastrointestinal tract infections
GUTI	Genitourinary tract infections
BI	Bone infections
CNSI	Central nervous system infections
BLDI:	Blood infections
FUO:	Fever of unknown origin
% F:	Percentage frequency

- **Frequencies of prescription categories according to diagnoses**
  - Of a total number of 104 cases of respiratory tract infections seen to be treated, 26.9%, 25.0% and 38.5% and 9.6% were respectively treated as infections with prescription categories A1, A2, B and F.
  - Of a total of 42 cases of gastrointestinal tract infections similarly diagnosed and treated, 14.3%, 38.1%, 31.0%, 2.4% and 2.4% were respectively treated as infections with prescription categories A1, A2, B, C and F prescriptions.
  - Cases of genitourinary tract infections treated were 36 in total. Of this total, 33.3% were treated with prescription category A1, 2.7% with prescription category A2, 36.1% with prescription category B and 11.1% with prescription category F.

- Cases of skin and soft tissue infections similarly treated totalled 88. Of all such cases, 15.9%, 2.3%, 29.5%, 3.4% and 1.1% were respectively treated with prescription categories A1, A2, B, C and of category F prescriptions.
- In total, 7 cases of bone infections were diagnosed and treated. The majority 42.9% of such cases, were treated with prescription category B followed by 28.6% of prescription category A1. No cases of diagnosed bone infections were treated with prescription categories A2, C and F.
- Of a total number of 12 cases diagnosed and treated as central nervous system infections, a majority 75.0% were treated with category B prescriptions and 8.3% each of prescription categories A2 and F prescriptions. No central nervous system infections were reported to be treated with category A1 prescriptions.
- All three (3) cases of blood infections diagnosed were treated with prescription category A1.
- Seventeen (17) cases of fevers of unknown origin were diagnosed and treated as infections with 52.9% and 41.2% of prescription categories B and A2. One out of 17 such cases (5.9%) was treated with prescription category A1.
- Of a number of 75 cases of non infectious diseases treated as current infections, 94.7% were treated with category F prescriptions.

- **Effect sizes of means of days of hospitalisation of patient groups diagnosed and not diagnosed with given infections (Table 4.1.8)**

  - Small differences between means of days of hospitalisation of patient groups diagnosed and not diagnosed with given infections as shown by indicated effects sizes and which may not be obvious to an observer were demonstrated by
    - non infectious diseases (effect size = 0.01),
    - fevers of unknown origin (effect size = -0.06),
    - genitourinary tract infections (effect size = -0.14) and
    - central nervous system infections (effect size = 0.25)
  - Medium differences obvious only to careful observers between means of days of hospitalisation of patient groups diagnosed and not diagnosed with given infections, that is differences as shown by indicated effects sizes, were demonstrated by

- respiratory tract infections (effect size = 0.40)
- gastrointestinal infections (effect size = 0.46)
- blood infections (septicaemia) (effect size = 0.58) and
- bone infections (effect size = - 0.61).

- **Impact of appropriateness of antibiotic prescribing on costs of antibiotic treatments**

Results of cost evaluations of patients' antibiotic treatments based on costs of antibiotics used in treatment of infections, costs of culture sensitivity tests and costs of hospitalisation are shown in Table 4.1.10 and summarised in Table 4.1.11. The evaluations as presented in these Tables show the cost distributions of antibiotic treatments as per prescription category at respective sites of study. Standard deviations as determined for mean costs of antibiotic treatments were found to be very large in most cases. This is attributable to observed substantial variations in costs of different types of antibiotics and also to large differences in costs of strengths and formulations of same antibiotics used in treating patients and is seen as compromising the practical usefulness of the measure of dispersion in assessing the impact of appropriate prescribing of antibiotics on costs of antibiotic treatments. In the opinion of the researcher, selections of types, strengths and formulations of antibiotics used in treating infections are all essential factors in determining the appropriateness of antibiotic prescriptions. For this reason, average costs of treatment were seen as directly reflective of how appropriately prescribers assessed patients and accordingly chose antibiotics in treating infections. For "testing purposes" therefore it was considered suitable to use "highest" versus "lowest" average costs of antibiotic treatment of patients treated with different categories of antibiotic prescriptions, as "indicators" in determining the impact of appropriateness of antibiotic prescribing on costs of antibiotic treatments.

Category A1 prescriptions

- Average cost of antibiotics per prescription for patients treated with antibiotic prescriptions classified in category A1 was R41.20 ±95.90 for all study sites. Highest and lowest average costs of R108.52±160.60 and R7.71 ±6.10 per prescription were recorded for the Queen II and Scott hospitals respectively.
- Average of total costs of antibiotic treatment, culture sensitivity tests and of hospitalisation of patients for the prescription category as determined for the five

hospitals was R129.68 ±144.09. Queen II and Scott hospitals contributed the highest and lowest total costs of R240.00 ±224.10 and R66.28 ±28.90 to this average.

Category A2 prescriptions

- Average cost of antibiotic treatment per prescription for patients treated with category A2 prescriptions was R27.79 ± 66.87 for all study sites. The highest and lowest average costs of R43.15 ± 111.68 and R6.25 ± 5.2 per prescription were respectively recorded for the Queen II and Maluti Hospitals.
- Average of total cost of antibiotic prescriptions, culture sensitivity tests, and of hospitalisation of patients for the prescription category as determined for the prescription grouping was 91.62 ± 92.29. The highest and lowest costs were recorded for Motebang and Maluti hospitals respectively as R106.86 ±67.80 and R68.25 ±53.60.

Category B prescriptions

- Average cost of antibiotic treatment per prescription for patients treated with the category of prescriptions was R105.33 ± 210.57 for all study sites. Queen II hospital contributed the highest cost of R190.67 ± 297.76 and Scott hospital the lowest cost of R18.35 ± 21.41 of antibiotic treatment per prescription to this average.
- Total costs of antibiotic prescriptions, culture sensitivity tests and of hospitalisation also averaged R237.52 ± 313.50 for patients treated with the prescription category group of all study sites. Queen II and Scott hospitals contributed the highest and lowest such costs in the values of R393.52 ± 425.36 and 105.39 ± 53.98 respectively to the this average.

Category C prescriptions

- All four (4) prescriptions classified in category C from the group of prescriptions studied came from the Queen II Hospital. Average cost of antibiotic prescriptions used in treating patients and total costs of treating infections as obtained for the group were R92.30 ± 60.30 and R459.00 ± 207.88 respectively.

Table 4.1.10 Percentage frequency distributions of prescriptions by category definitions and according to study sites and costs of prescriptions

Study site	Frequency distributions of costs of treatment by prescription categories according to study sites									
	n	Total costs of Antibiotic prescriptions (Rands)	Average cost of Antibiotic prescriptions (Rands)	Total costs of treating infections) (Rands)	Average of total costs of treating infections (Rands)	n	Total costs of Antibiotic prescriptions (Rands)	Average cost of Antibiotic prescriptions (Rands)	Total costs of treating infections) (Rands)	Average of total costs of treating infections (Rands)
	Prescription category A1					**Prescription category A2**				
Berea	6	103.66	17.30 ±17.2	503.66	83.94±37.80	4	108.98	27.25 ±50.0	308.98	77.24±57.9
Maluti	10	109.79	11.00±8.40	671.50	67.15±37.90	5	31.25	6.25±5.2	341.26	68.25±53.6
Motebang	16	261.89	16.40±17.40	1647.67	103.00±60.80	10	427.64	42.76±49.2	1068.64	106.86±67.8
Queen II	16	1736.32	108.52±160.60	3846.09	240.00±224.10	13	560.92	43.15±111.68	1377.69	106.00± 147.8
Scott	7	53.98	7.71±6.10	463.98	66.28±28.90	12	94.49	7.87±8.77	934.49	77.87±52.61
Total	55	2265.64	41.20±95.90	7,132.90	129.68±144.09	44	1222.98	27.79±66.87	4031.06	91.62±92.29
	Prescription category B					**Prescription category C**				
Berea	14	710.65	50.76±89.81	1869.93	133.47±161.95	0	0.00	0.00	0.00	0.00
Maluti	9	371.78	41.30±87.47	1161.78	129.08±103.47	0	0.00	0.00	0.00	0.00
Motebang	21	1178.72	56.13±47.43	3238.72	154.22±88.48	0	0.00	0.00	0.00	0.00
Queen II	38	7245.64	190.67±297.76	14527.24	393.52±425.36	4	369.19	92.30±60.30	1839.19	459.80±207.88
Scott	10	183.54	18.35±21.41	1053.91	105.39±53.98	0	0.00	0.00	0.00	0.00
Total	92	9690.33	105.33±210.57	21851.58	237.52±313.50	4	369.19	92.30±60.30	1839.19	459.80±207.88
	Prescription category F									
Berea	5	258.29	51.65±55.67	713.07	142.61±312.71					
Maluti	4	72.30	18.08±19.14	552.30	138.07±114.88					
Motebang	13	317.54	24.43±25.8	2036.54	156.66±145.05					
Queen II	31	1200.06	38.71±71.02	4380.40	141.30±115.51					
Scott	2	15.84	7.92±4.41	175,84	87.92±4.41					
Total	55	1864.03	33.89±106.38	7858.15	142.88±117.95					
Percentage ratio of costs of category F prescriptions to total costs of categories A1, A2, B, C and F prescriptions = 12.1%										

Table 4.1.11 Costs of antibiotic treatment by prescription categories

Prescription category	Number of prescriptions in category	Costs of treatment			
		Total cost of antibiotic prescriptions for prescription category (Rand)	Average cost ± standard deviation of antibiotic prescription for prescription category (Rand)	Total cost of treating infections in patient groups treated with given prescription category (Rand)	Average of total cost ± standard deviation of treating infection in patient groups treated with given prescription category (Rand)
Prescription Category A1	55	2265.64	41.20±95.90	7132.90	129.68±144.09
Prescription Category A2	44	1222.98	27.79±66.87	4031.06	91.62±92.29
Sub total (A1 +A2)	**99**	**3488.62**	**34.50**	**11163.96**	**110.65**
Prescription Category B	92	9690.33	105.33±210.57	21851.58	237.52±313.50
Prescription Category C	4	369.19	92.30±60.30	1839.19	459.80±207.88
Prescription category F	55	1864.03	33.89±106.38	7858.15	142.88±117.95
Total	250	15412.17	61.65	42712.88	170.85

Calculated "d - values"

Formula: d-value = $(\mu_1 - \mu_2)/\sigma^*$ where μ_1 and μ_2 are mean costs of antibiotic treatment for patient groups treated with respective antibiotic prescription categories and σ^* the maximum of the two standard deviations of the two compared groups

Mean costs of prescribed antibiotics per prescription

Compared groups	**d - values**
A1 and A2	0.14
A1 and B	- 0.30
A2 and B	- 0.37

Mean total costs of treating infections in patient groups

Compared groups	**d - values**
A1 and A2	0.26
A1 and B	- 0.34
A2 and B	- 0.47

Comparisons of costs of antibiotic prescription groups

Grouped together, prescription categories A1 and A2 are considered antibiotic prescriptions categorised as appropriately written prescriptions for treating infections with absolute and suspected bacterial aetiologies. The average cost of antibiotics prescribed per prescription in the cases of these two prescription category types was R34.50 (Table 4.1.11).

- By comparison the average cost of antibiotics prescribed per prescription in the category of antibiotic prescriptions considered appropriately written (prescription categories A1 and A2) is less than the average cost of antibiotics prescribed per prescription in the category of antibiotic prescriptions considered inappropriately prescribed (prescription category B) by a difference of R70.83.
- The average cost of R110.65 of hospitalisation and antibiotic treatment of patients treated with antibiotics prescribed on prescription categories A1 and A2 by comparison again is lower than the average cost of R237.52 of hospitalisation and antibiotic treatment of same patient groups treated with antibiotics prescribed on prescription category B by R126.87.
- Average cost of R459.80 of hospitalisation and antibiotic treatment of patients treated with category C antibiotic prescriptions is higher than average costs respectively of R110.65 and R237.52 of antibiotic prescriptions classified in categories A1 and A2 on one hand and category B on the other hand by as much as R349.15 and R222.28 respectively
- Effect sizes (d - values) for differences of the average or mean total costs of antibiotic treatment and hospitalisation for patient groups treated with prescription categories A1 and A2", "A1 and B" and "A2 and B" were 0.26, -0.34 and -0.47.

- **Estimated cost of antibiotic "wastage" in wards**

Percentage ratio of costs of category F prescriptions to total costs of categories A1, A2, B, C and F prescriptions, was determined as 12.1%. This by interpretation is the percentage "cost of antibiotics wasted" in treating patients on account of antibiotics classified in category F being prescribed for clinical conditions in which bacterial infections were absolutely not aetiologies.

4.1.1.2.2 Results Evaluation and Discussion

- **Use of indicators in defining patients' response to antibiotic treatment**

Treatment indicators used for patients' response to the treatment of their infections were "improved" or "not improved" as defined in Section 3.2.1. Death of a patient .as indicated was not necessarily considered as an indicator of non-response to antibiotic treatment because of other factors that may have complicated patients' death in a hospital. As mentioned in Section 3.2.1, the state of a patient's condition at the time of admission for an infectious disease could be a determinant of whether or not such a patient could be successfully treated with antibiotics. A patient could also die during the course of antibiotic treatment from other clinical conditions unrelated to the infection being treated. Ignoring "death" as an indicator of non-response of antibiotic therapy rationally simplifies the assessment of impact of appropriateness of antibiotic prescribing on treatment. Despite this however, it cannot be ruled out completely that the indicator did not account for patients' non-response to antibiotics used in treating their infections. It is possible for a patient dying from a serious infection, for example septicaemia, to be saved following timely hospital admission if the appropriate antibiotics are used amidst other necessary therapeutic measures employed in managing the patient. Kollef (2000:S133), writing on inadequate antimicrobial treatment as an important determinant of outcome for hospitalised patients, made reference to Leibovici *et al.* (1998) and Weinstein *et al.* (1997) as both demonstrating a positive impact of appropriate antibiotic treatment in septicaemia. Both research groups, according to him, showed in their different studies that hospital mortality rates were significantly lower for patients with blood stream infections who received adequate antimicrobial treatment than for those who received inadequate treatment. In view of this consideration it was found necessary to determine treatment success rates in patients receiving antibiotic treatments as a range between two rates in which numbers of patients dying during course of such treatments were included and excluded in the total number of patients used in the determinations. Including numbers of patients dying during the course of antibiotic treatments in the total number of patients receiving the treatment as used in determining treatment success rates, gives the lower rate of the range while excluding the number of patients who died from the total number of patients receiving indicated treatments in a second determination would produce an upper rate for the range.

- **Impact of appropriateness of antibiotic prescribing on treatment outcomes**

From calculated treatment success rate determinations as shown in Table 4.1.5 patients treated with antibiotic prescriptions considered appropriately written based on principles of antibiotic prescribing for cases in which bacterial infections were absolute aetiologies (category A1 prescriptions), predictably produced the most significant improvement in their response to antibiotic treatment. Lower treatment success rate determinations showed patients treated with category A2 prescriptions exhibiting poorer response to their treatment than patients receiving category B prescriptions. This observation by interpretation indicates the impact of the prescribing antibiotics for cases for which bacterial infections were not aetiologies. This, however, could be true if deaths indeed are indicators of patients' non-response to antibiotic treatment. As speculated it could probably be, at least, in some cases. The poorer response of patients receiving category A2 prescriptions in such cases could in those circumstances be reasonably attributed to prescribed antibiotics not having any therapeutic effect on non-bacterial infection related clinical conditions for which antibiotic prescriptions were given. This is meant to imply that antibiotics were used to treat cases for which they were not indicated instead of patient care efforts being directed in the use of other treatment options. Proof of this statement, however, is beyond the scope of this research since in its design, collection and analysis of data on parallel treatment patients might be given was not included. The observation on the other hand is discounted if upper rates of determined group treatment success rates which excluded deaths as indicators for patients' non-response to antibiotic treatment are used in comparing the effectiveness of antibiotic treatments in the three prescription category groupings of patients. Patients receiving treatments with antibiotic prescriptions classified in category A2 demonstrated higher response rates to treatment than patients receiving treatment with category B prescriptions.

Using relative treatment success rates as measures of effectiveness of antibiotic treatment in the respective prescription categories, patients who received treatment with category A1 prescriptions have been shown to demonstrate the highest response to their antibiotic treatment in comparison to patients who received, in that order, antibiotic treatment classified in categories A2 and B (Table 4.1.5). A slight difference of 0.08 was seen to exist in the calculated relative treatment success rates of prescription categories A1 and A2 if upper range determinations that excluded death as an indicator for patient non-response to antibiotic treatment were considered. Though this could be considered

negligible, it does in a way give some credence to the speculated negative impact of antibiotic prescribing in likely cases where bacterial infections are not aetiologies on the overall treatment response of groups of patients given such prescriptions. The almost negligible difference in the calculated relative treatment success rates for prescription categories A1 and A2 highlights the similarities in treatment outcomes of antibiotics prescribed appropriately in accordance with antibiotic prescribing principles. The 0.94 relative therapeutic success rates determined for patients treated with prescription category B significantly apportioned lower rates of effectiveness to prescriptions in this category in comparison with those in categories A1 and A2 in situations where death of patients in the course of receiving antibiotic treatment is not considered an indicator of patient non-response to treatment. Use of relative treatment success rates allowed for a more precise determination of comparative effectiveness of antibiotic treatment within defined prescription categories.

Results of these assessments have suggested that appropriate antibiotic prescribing may have positive impact on patient's response to antibiotic treatment. A search of the literature has not revealed similar results of any research work that investigated appropriateness of antibiotic prescription on treatment outcomes in a way as was carried out in this study. The findings of Leibovici *et al.* (1998) and Weinstein *et al.* (1997) as quoted by Kollef (2000:S133) and referenced above can be taken as providing documented evidence that appropriate prescribing of antibiotics can have a positive impact positively on antibiotic treatment outcomes.

The 100% improvement recorded in patients given antibiotics prescribed on the basis of culture sensitive test results, though determined for only four (4) patients who were treated with this category of prescriptions, gave an indication of high probabilities of high treatment success rates being achieved in patients given antibiotic prescriptions based on culture sensitivity test results (Table 4.1.5).

- **Inferences from statistical correlations**

Comparative assessment of relative treatment success rate determinations for patient groups treated with different antibiotic prescription categories showed that appropriate antibiotic prescribing according to principles may have a positive impact on patients'

response to antibiotic treatment. Results of statistically determined relationships between appropriateness of antibiotic prescribing and patients' recovery status in this study however showed only a weak positive relationship between the two variables. Utts and Heckard (2007:167) described a correlation coefficient of +0.74 (Pearson) as a "somewhat" strong positive relationship. For phi, a coefficient of 0.5 is considered large and significant. Compared to these values the contingency, phi, and Cramers' V coefficients respective values of 0.1902, 0.1938 and 0.1370 as determined, are considered too small for interpretation as a significant relationship between appropriateness of antibiotic prescriptions and patient recovery. Stated differently, the low coefficients can be interpreted to mean a non-existence of a statistically strong relationship between appropriateness of antibiotic prescribing and patient recovery status.

The statistically weak relationship observed between patient recovery and antibiotic treatments prescribed in manners as investigated, can be explained when effects of other factors on drug treatment outcomes are considered. Patients' recovery in response to drug treatment can be attributed to factors additional to the quality of drug treatment they receive. In antibiotic treatments, factors like the severity of infection, the sensitivities of infecting pathogens to administered antibiotics and the regularity, likewise routes by which prescribed antibiotics are administered in the opinion of the researcher, may all determine the nature of patients' clinical response to antibiotic treatment and influence accordingly relationships between appropriateness of antibiotic prescribing and patient recovery.

With this explanation, and despite the statistically weak relationship between the two variables, the calculated treatment success rates were seen to suggest some degree of positive association between appropriateness of antibiotic prescribing and patients' response to antibiotic treatment. These, as reported in earlier paragraphs, demonstrated patient groups treated with prescription categories A1 showing better responses to their treatments than patient groups treated in that order with prescription categories A2 and B (Table 4.1.5),

- **Impact of appropriateness of antibiotic prescribing on patient's days of hospitalisation**

Patients treated with prescription category B spent more days in hospital on the average than patients treated with prescription categories A1 and A2 (Table 4.1.6). This indicates that appropriate antibiotic prescribing may have a positive impact on the number of days patients stay in hospital.

Patients treated with prescription category C, though treated with antibiotics that were prescribed based on results of culture sensitivity tests, spent on the average more days on hospital admission than patients treated with prescription category B to whom antibiotics were empirically and inappropriately prescribed. This, most possibly, could be attributed to severer infections being treated in the patient group than in patient groups treated with category B prescriptions. In addition to this, it could also be attributed to the manner in which the antibiotics were prescribed for the group. Determined from inpatient antibiotic prescription records analysed for their appropriateness, all four prescriptions comprising prescription category C which all came from the Queen II Hospital (Table 4.1.2) were seen to be prescribed according to results of culture sensitivity tests performed after initial antibiotic treatment failures. This manner of antibiotic prescribing contravenes principles of antibiotic prescribing according to Archer and Polk (2005:795) and Rees and Betts (1996:1059). By the authors' indications, it is required in principle for clinical specimens for culture and sensitivity testing to be obtained before the initiation of antibiotic therapy in the treatment of infections needing antibiotics to be prescribed according to culture sensitivity test results. Revision of the initial antibiotic therapy in such instances can be done when results of the culture sensitivity tests becomes available.

The time of initiating antibiotic therapy appropriate for treating a given infection is postulated to largely determine how early patients treated for the infection will improve and get discharged from hospital. This postulate being true, the observed manner of antibiotic prescribing in patients treated with category C prescriptions as indicated above would be seen to delay the recovery of the patient group from their treated infections. Manners in which antibiotics were prescribed for the patient group viewed from this perspective can be seen to partly account for the longer days the patient group spent in

hospital and to demonstrate a negative impact of non adherence to principles of antibiotic prescribing in patient recovery and days of hospitalisation.

Effect size determinations (Table 4.1.8) showed no practically significant differences between mean days of hospitalisation of patients diagnosed and not diagnosed with non infectious diseases, fevers of unknown origin, genitourinary tract infections, central nervous system and respiratory tract infections since d-values were in absolute value smaller than 0.5, where d = 0.2 is regarded as a small effect (Cohen, 1988). According to this interpretation, these infections were not seen to influence significantly lengths of patients' stay in hospital for their treatment. In other words patients' response to antibiotic treatments of these infections and hence lengths of their stay in hospital, would probably depend more on the effectiveness of prescribed antibiotics than on characteristic prognoses or natures of the infections.

Effect size values (Table 4.1.8) for differences in the means of days of hospitalisation of patient groups diagnosed and not diagnosed with gastrointestinal, blood, bone, skin and soft tissue infections were in the region of 0.5 which is regarded as a medium effect (Cohen, 1988). By interpretation, differences in the means of days spent in hospital by patients diagnosed and not diagnosed with these infections can barely be noticed by an observer (Utts & Hackard (2007:583). Patients' recovery from these infections and hence their lengths of stay in hospital by implication are influenced to some extent by the nature or the prognoses characteristic of these infections. Stated differently, patients' days of hospitalisation for the treatment of these infections may be longer for reasons partly attributable to prognoses characteristic of these infections and not entirely on the effectiveness or appropriateness of prescribed antibiotics.

Patients treated for skin and soft tissue infections showed the largest effect size of 0.71 (0.80 is regarded as a large effect according to Cohen (1988) for differences of mean days of hospitalisation of patients diagnosed and not diagnosed for the infection. In comparison with other infections, patients treated for skin and soft tissue infections are most likely to stay on hospital admission for the longest number of days on the average irrespective of the effectiveness of antibiotics prescribed for the infection. This, to some extent, is expected considering that skin and soft tissue infections, as exemplified by infected wounds, generally involve damaged tissue that need to heal as part of the

process in patients' recovery from this infection. While antibiotics used in treating the infection type may effectively eradicate and keep at bay implicating pathogens, the actual healing process of damaged tissue may be long enough to prolong patients stay in hospital.

In the categories of patients treated for gastrointestinal, blood, bone and skin and soft tissue infections, these observations imply that the impact of appropriateness of antibiotic prescribing on days of hospitalisation can be best realised if comparison of mean days of hospitalisation for patient groups treated with respective antibiotic categories is carried out for patients treated for same diagnosed infections. Such comparisons were made for patient groups treated with prescription categories A1, A2 and B for respective infections (Table 4.1.9). Comparisons of percentage frequencies of patients treated with respective prescription categories showed that, for each infection type, the highest percentage of patients treated with antibiotics, were treated with category B prescriptions. This is in exception of gastrointestinal infections, where patients treated with category A2 prescriptions constituted the highest percentage of the total number of patients treated for the infection. (Table 4.1.9). Compared with patient groups treated with categories A1 and A2 prescriptions, patient groups treated with category B prescriptions in respective cases of infections spent on the average the highest number of days in hospital. This indicates, as established in earlier result interpretations, that appropriate prescribing of antibiotics may have a positive impact on days of hospitalisation.

- **Impact of appropriateness of antibiotic prescribing on costs of antibiotic prescriptions**

- **Assumptions and parameters for cost estimates**

Severity of infections may determine type and formulation and hence cost of antibiotics used in treating infections. Lack of documentation on this characteristic of treated infections did not allow for analysis of data to be done to account for effects of severity of infections on appropriateness and costs of antibiotic prescriptions. In determining the impact of degrees of appropriateness of antibiotic prescriptions on costs of antibiotic treatment however, it was assumed that the chances of antibiotics being prescribed by a group of prescribers in a given clinical environment in accordance with or without

adherence to antibiotic prescribing principles in both severe and less severe cases will be the same since factors affecting the prescribing behaviour of the given group of prescribers remain the same each time an antibiotic is prescribed. The same is considered true in cases of antibiotic dosage forms and doses of antibiotics prescribed in the treatment of patients. Dosage forms and doses of antibiotics used in the treatment of infections, for reasons of prescribers' desire to achieve antibiotic plasma concentrations that would ensure the effectiveness of such treatment, are most likely to be selected according to the severity of the infections (Bishai, 2002:843). In other words when treatment options are considered in cases of both severe and less severe infection antibiotic doses and dosage form selections inclusive, there are equal chances of these drugs being prescribed in accordance with or without adherence to antibiotic prescribing principles by a given group of prescribers within a given clinical environment. As one of the criteria used in the assessment of prescriptions the study also included the conformity of antibiotic prescriptions to doses of prescribed antibiotics. Unusual doses of antibiotics were considered correct or incorrect depending on prevailing clinical conditions for which they were prescribed for individual patients.

Consideration was also given to severe and special cases of septicaemia from the perspective of their contributions to cost estimates of antibiotic prescriptions. Septicaemia as a clinical condition may change pharmacokinetic parameters of administered antibiotics (Pinder *et al.*, 2002: 132 & 134). This may create situations where higher doses of antibiotics may be required to result in unusually high costs of antibiotics being used in treating patient groups with the infection. Pathophysiological changes in septicaemia according to Pinder *et al.* (2002:132) result in increased creatinine clearance and increased volumes of distribution to cause low serum antibiotic concentrations. This, they further indicated, may be offset by ensuing renal and hepatic impairment which are also associated with conditions of septicaemia. At different stages of the disease process according to the authors' indications, antibiotic requirements of septicaemic patients may be similar, less or greater than those of the conventional ward patient. What these translate into in principle, is for prescribers under the described clinical scenario to prescribe antibiotics in manners that would take into account antibiotic dosage adjustments as would be required for septicaemic patients. Essentially, this boils down to prescribers' adherence to principles of antibiotic prescribing in this category of patients as the study investigated. Also, only five prescriptions out of 297

prescriptions that were written for diagnosed cases of infections were prescriptions for septicaemia (Table 4.1.17). It is assumed that what effects costs of such prescriptions may have on cost estimates of prescribed antibiotics, may not change significantly reported results of the study.

With these cost assumptions patterns of appropriateness of antibiotic prescriptions as established in the study were taken as not to be affected significantly by severity or types infections treated.

On the basis of administrative policies applying to the charging of hospitalised patients at respective study site hospitals, it was found appropriate to base cost evaluations of antibiotic treatment on costs of antibiotics, culture sensitivity tests (if performed) and costs of hospitalisation. At the time of data collection and for periods previous to January 2008, patients were charged flat subsidised rates of R10.00 for each day they spent on admission at both government and CHAL hospital study sites. Contrary to government hospitals where patients were charged flat rates of R3.50 for all drugs used in treating them while on admission, drugs are non-levied items at CHAL hospitals for which both inpatients and outpatients do not pay. This was according to information obtained from interviews of Heads of Patient Billing Sections of Queen II and Scott Hospitals, (2009), in absence of gazetted information or other literature of reference. Other costs, e.g. costs that may be incurred with respect, for example, to antibiotic reconstitution in parenteral antibiotic administrations or extra nursing and medical services patients may receive, are not factored into cost determinations of services rendered to inpatients. These accordingly are not considered in determining total costs of antibiotics and hospitalisation. These are considered "silent costs" which if factored into the processes of cost determinations may only reflect as higher total costs of hospitalisation and parenteral antibiotic formulations as reported. It may not, in fact, change the overall observed patterns of effects of degrees of appropriateness of antibiotic prescribing as the study investigated. To be able to compare costs of antibiotic treatments among study site hospitals, a standardised method in evaluating antibiotic treatment costs was used in cost determinations for all study site hospitals. Cost determinations by this standardised method involved the use of costs of antibiotics as invoiced to hospitals by the National Drug Service Organisation (NDSO) and also costs

of hospitalisation and laboratory fees as determined from stipulated hospital fee structures by the Ministry of Health and Social welfare (MOHSW) and CHAL.

The purpose of this aspect of the study is to establish whether inappropriate prescribing of antibiotics affects costs of treatment for which the drugs are used. Basing cost evaluations of antibiotic treatments on the actual cost of the drugs, costs of culture sensitivity tests and costs of hospitalisation is considered adequate in producing cost estimates of antibiotic treatments that can be analysed for an assessment of the impact of appropriateness of antibiotic prescriptions on costs of treating infections. An antibiotic inappropriately prescribed connotes the incurrence of a cost component of treating an infection that is reflective of the actual cost of the inappropriately prescribed antibiotic. Culture sensitivity tests increase costs of antibiotic treatment. They do expectedly, however, help in making antibiotic choices that more effectively treat infections with better treatment outcomes and consequent reductions in other components of total treatment costs. Patients' days of stay in hospital, and hence costs of hospitalisation may increase with treatment failures resulting from inappropriate prescribing of antibiotics.

- **Cost assessments of antibiotic prescription categories**

Costs of antibiotic treatments demonstrate wide dispersions from patient to patient as judged from standard deviation determinations of calculated means of costs of treatment. This in practice is expected as all patients treated with infections at hospitals under normal circumstances are not given the same type of treatment in which case a normal distribution of percentage frequencies of treated subjects according to treatment response or treatment characteristic indicators including costs of drugs used may be expected. Absolute values of average or mean costs, however, are reflective of the total costs of antibiotics used and the way they have been prescribed with respect to the need of their use, their selection, doses used and the length of time for which they have been used in treating a given group of patients. This in totality will reflect on how appropriately the drugs have been prescribed and can hence be used in determining the effect on costs on the degree of appropriateness of such prescriptions.

Average costs of antibiotic treatments as results report are lowest for groups of patients treated with antibiotic prescriptions in category A2 (R27.79 ± 66.87) and followed in that

order by prescription categories A1 (R41.20 ± 95.90), C (R92.30 ± 60.30) and B (R105.33 ± 210.57). Average costs of hospitalisation was similarly lowest for patients treated with antibiotic prescriptions in category A2 (R91.62 ± 92.29) followed in that order by prescription categories A1(R129.68 ± 144.09), B R237.52 ± 313.50 and C(R459.00±207.88). Considered together as categories of antibiotic prescriptions appropriately written according to principles, average costs of antibiotics prescribed for patient groups treated with prescription categories A1 and A2 (R34.50 ± 95.90) were lower than average costs of antibiotics prescribed for the patient treated with category B prescriptions (R105.33 ± 210.57). Total costs of hospitalisation (R110.65) for patient groups treated with category A1 and A2 prescriptions were similarly lower in comparison with the patient group treated with category B prescriptions.

Effect sizes (d-values) determined for differences between average costs of prescribed antibiotics per prescription or average total costs of antibiotic treatment and hospitalisation for patient groups who received antibiotic treatment on prescription categories "A1 and A2" was smaller than 0.2 (Foot notes: Table 4.1.11). Differences between average costs of antibiotic prescriptions categorised as A1 and A2 by this effect size determination was of no practical significance. Effect sizes for differences between average costs of prescribed antibiotics per prescription of antibiotic treatment and hospitalisation for patient groups who received antibiotic treatments respectively on prescription categories "A1 and B" and "A2 and B" were however greater than 0.2 but still not large enough to be regarded as medium effect (Foot notes: Table 4.1.11).These were considered small effects according to Steyn (2009:4-21) and Utts and Hackard (2007:582) and may be interpreted as statistically insignificant. For average total costs the differences between means of prescription categories A1 vs. A2 and A1 vs. B also can be regarded as having no practical significance. In the contrary, the difference between the means of A2 vs. B has a medium effect, since its effect size value is near 0.5, which is regarded as a medium effect (Cohen, 1988). It is difficult explaining the observed significant differences between the means of costs of category A2 and category B prescriptions in absence of any such differences being noticed in the case of category A1 and category B prescriptions. This said, however, and considering that average costs of categories of prescriptions demonstrate a trend in which average costs of category B prescriptions were greater than average cost of category A1 prescriptions which, in turn, were greater than average cost of category A2 prescriptions, a significant

difference between average costs of categories B and A2 prescriptions which are at the extremes of the observed trend could be expected. In spite of the above interpretation, the larger effect sizes for the differences between average costs of antibiotic treatment observed for patient groups treated with the respective prescription categories as considered can be taken as being of some practical importance with respect to treatment costs that were incurred when antibiotics were prescribed appropriately and inappropriately. The the extent to which antibiotics are appropriately prescribed for inpatients are observed by these findings have to some extent positively impacted on costs of treatment of infections determined either as costs of prescribed antibiotics or costs of patients' hospitalisations.

.

The average cost of treating patients with antibiotic prescriptions in category C, that is, antibiotic prescriptions in which selections of prescribed antibiotics were based on culture sensitivity test results, is comparatively much higher than those of prescription categories A1 and A2 but lower than that of prescription category B. Similarly, average cost of hospitalisation of patients treated with category C antibiotic prescriptions is much higher than average costs of hospitalisation of patients treated empirically for infections with antibiotic prescriptions considered appropriately and inappropriately prescribed. These differences in costs of antibiotic treatment and hospitalisation of patients treated with the indicated categories of prescriptions may be considered as signifying the impact of the practice of prescribers requesting for culture sensitivity tests only after failures of initial antibiotic treatments on total costs of inpatients treatment for infections. A majority 69.4% of respondents to questionnaires in Phase III of this study who have laboratory facilities and practice in inpatient settings, admitted requesting for culture sensitivity tests (CST) only after treatment failures (Section 4.3.4, Table 4.3.21). Additional to the disadvantage of causing suppression of growth of pathogenic bacteria possibly causing infections (Scottish Infections Standards and Strategies Group, 2003:282; Bronska *et al.* 2006:137; Popa *et al.,* 2009:227) the practice of requesting for CST only after treatment failures has the disadvantage as established by results of this study, of resulting in increased costs of antibiotic treatment and hospitalisation of patients. This is particularly envisaged in the case of skin and soft tissue infections, which results of this study established as inherently associated with long hospital stays. Three out of the four cases treated with category C prescriptions were actually cases of skin and soft tissue infections (Table 4.1.7). The observed high antibiotic treatment and hospitalisation costs

of treating patients with these prescriptions may be attributed mostly to the nature of the infections that were treated with these prescriptions and perhaps the impact of prescribers' failure to make their initial antibiotic choices based on CST results.

Average costs of antibiotics used in treating patients were observed to be higher generally for government than for CHAL hospitals. This most probably reflects the impact of degrees of inappropriate prescribing of antibiotics on costs of antibiotic usage in the two types of health institutions. Inappropriate prescribing of antibiotics was observed to be comparatively more prevalent in government than in CHAL hospitals. As speculated in result evaluations and discussion presented in Section 4.1.1.1 the observed less inappropriate prescribing of antibiotics in CHAL than in government hospital could be attributed to effects of prescribers' adherence to possible internal policies that advocate stricter and hence more appropriate use of antibiotics in the former than in the latter categories of study site hospitals.

- **Antibiotic wastage resulting from prescribing for unjustified clinical reasons**

An amount of R1,864.03, being the cost of antibiotics prescribed for clinical conditions deemed not justified for antibiotic use had been determined (examples of category F prescriptions as prescriptions given for clinical conditions for which the prescription of antibiotics were considered not justified are provided in Appendix 5). This is considered the cost of antibiotics wasted during the one-month period of this study on the basis of their being inappropriately prescribed for unjustified reasons. It represented 12.1% of a total cost of R15,412.17, which was the cost of the total number of inpatient antibiotic prescriptions that had been prescribed during the study period for the treatment of infections. Among the five study site hospitals this works up to an amount of R22,368.36, that could be possibly wasted from an annual budget on account of inappropriate prescribing of antibiotics for unjustified reasons. This wastage is considered significant if viewed from the perspective of Lesotho. The country, despite its classification among resource limited countries of the world by world economic ratings (World Bank, 2008:1), operates a health delivery system in which drug budgets of its public health institutions are nearly fully financed by the institutions themselves without significant rebates from the consuming public The sustenance of such a health delivery system requires meticulous use of resources and a 12.1% of the cost of a class of drugs used in treating a given clinical condition seen as being wasted on account of inappropriate prescribing

should be considered a significant problem in the health delivery system that warrants serious attention.

4.1.1.3 Determining patterns and effects on treatment outcomes of multiple antibiotic prescribing in wards.

The section presents results of inpatient antibiotic assessments to determine the extent to which prescribers use multiple antibiotic therapies in treating infections, associations of multiple antibiotic therapy with appropriateness of antibiotic prescribing and effects of single and multiple antibiotic therapies on antibiotic treatment outcomes. Results are evaluated to establish patterns of multiple antibiotic prescribing among inpatients of study site hospitals while discussions were done in line with literature opinions and cross references to results of other sections of the study to predict the expected impact of the practice of multiple prescription of antibiotics on the appropriate use of this class of drugs and the general effects on treatment outcomes.

4.1.1.3.1 Results

Percentage frequency distribution of numbers of antibiotics prescribed per prescription in treating infections among inpatients at respective study sites is shown in Figures 4.1.3 and 4.1.4. The extent of multiplicity of antibiotic prescribing in treating this group of patients are shown in Table 4.1.12 in which frequencies of numbers of antibiotics often prescribed per prescription at given study sites is shown. Table 4.1.13 similarly shows frequencies of numbers of antibiotics prescribed per prescription in established categories of antibiotic prescriptions.

- **The extent of prescribers' use of multiple antibiotic therapies in treating infections**

Of total 307 prescriptions assessed,

- 44.3% and 32.9% were respectively prescriptions with one (1) and two (2) prescribed antibiotics, giving 77.2% in total as prescriptions with one (1) or two (2) prescribed antibiotics;
- 16.0% and 6.2% were prescriptions with three (3) and four (4) prescribed antibiotics and similarly giving 22.2% in total as prescriptions with three (3) or four (4) respectively contributing to this total; and

- two (2) prescriptions only representing 0.65% of total prescriptions assessed had more than four (4) prescribed antibiotics.
- Other observed patterns of multiplicity of antibiotic prescribing at various study hospitals have shown that,

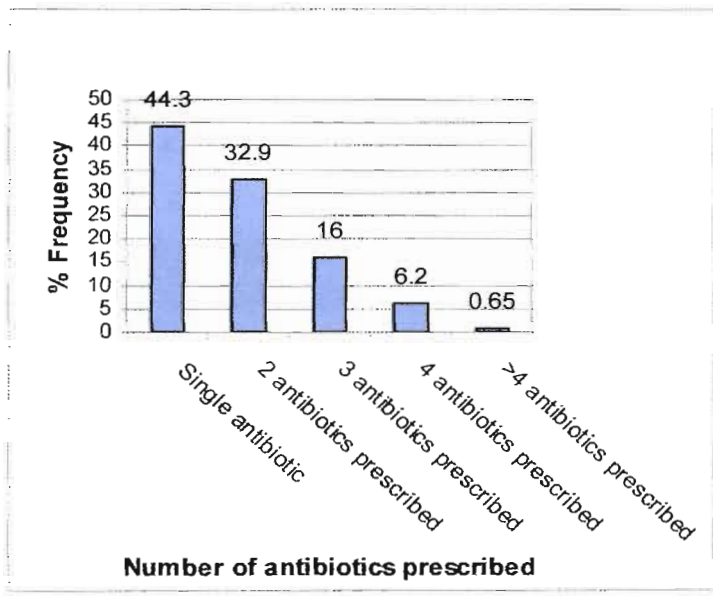

Figure 4.1.3 Percentage frequency distributions of numbers of prescribed antibiotics per prescription used in treating infections among inpatients

Table 4.1.12 Percentage frequency distribution of prescriptions by study site and according to number of prescribed antibiotics

Study site	Frequency of prescriptions according to number of prescribed antibiotics										
	Single antibiotic prescribed		2 antibiotics prescribed		3 antibiotics prescribed		4 antibiotics		> 4 antibiotics prescribed		**Total**
	n	n%	n	n%	n	n%	n	n%	n	n%	n
Berea	16	51.6	7	22.6	6	19.4	2	6.5	0	0.0	31
Maluti	18	50.0	12	33.3	2	5.6	4	11.1	0	0.0	36
Motebang	41	46.1	35	39.3	7	7.9	6	6.7	0	0.0	89
Queen II	44	37.9	32	27.6	31	26.7	7	6.0	2	1.7	116
Scott	17	48.6	15	42.9	3	8.6	0	0.0	0	0.0	35
Total	136	44.3	101	32.9	49	16.0	19	6.2	2	0.65	307

Notation: n% value calculations based on row totals

- of the respective total number of prescriptions assessed for each study site hospital, prescriptions with one prescribed antibiotic presented the majority of all prescriptions assessed, being 51.6% for Berea hospital, 50.0% for Maluti hospital, 48.6% for Scott hospital, 46.1% for Motebang hospital and 37.9% for Queen II hospital. They were followed respectively and in that order for each site, with prescriptions with two, three, four and more than four prescribed antibiotics;
- a comparison of relative frequencies of distributions of numbers of prescribed antibiotics per prescription as shown in Figure 4.1.4, demonstrates a trend in antibiotic prescribing at all study sites that exhibited generally greater inclination of prescribers towards the use of fewer numbers of antibiotics in treating infections;
- the smallest percentage frequency of 37.9% of antibiotic prescriptions with one (1) prescribed antibiotic as well as the highest percentage frequency of 26.7% of antibiotic prescriptions with three (3) prescribed antibiotics were respectively seen at the Queen II hospital, the biggest study site hospital with referral status;

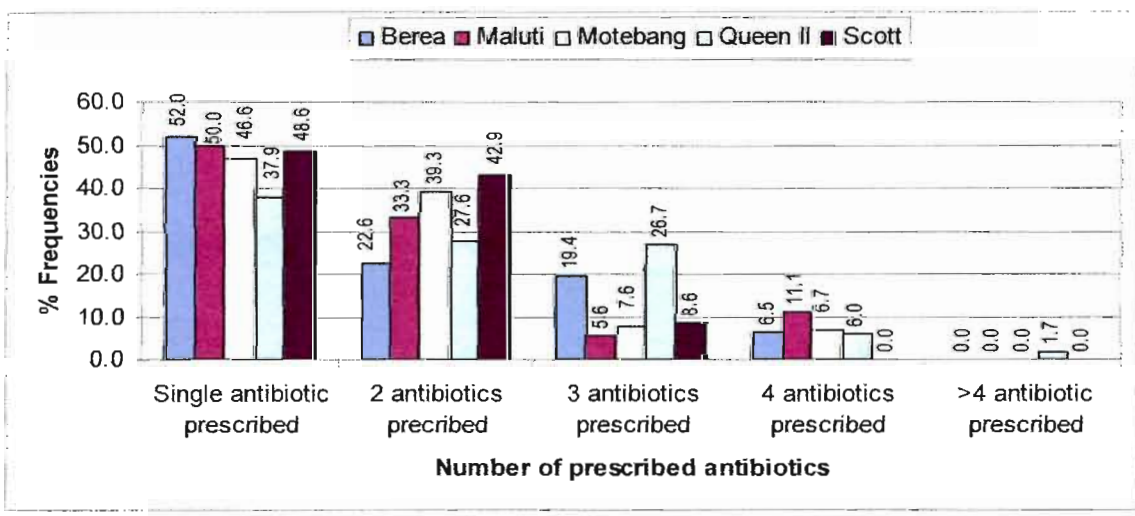

Figure 4.1.4 Percentage frequencies of number of prescribed antibiotics per prescription at study sites

- the only two prescriptions for which the number of prescribed antibiotics was more than four, were also encountered at the Queen II hospital; and
- prescribers at the referral hospital generally demonstrated higher tendencies to treat inpatients diagnosed with infections with higher numbers of antibiotics than prescribers in other hospitals.

♦ Associations of multiple antibiotic therapies with appropriateness of antibiotic prescribing

As Table 4.1.13 and Figure 4.1.5 show, variations in relative frequencies of antibiotic prescriptions with differing numbers of prescribed antibiotics are seen to exist within categories of antibiotic prescriptions. Examples of prescribed antibiotics as categorised in respective antibiotic prescription category groupings are provided in Appendix 5)Important findings of note in respect to relative frequencies of distribution of prescriptions with given numbers of antibiotics within prescription categories include the following:

- **Prescriptions with one (1) prescribed antibiotic**

- Single antibiotics were seen to be prescribed at appreciably high frequencies in all prescription categories except in prescription category C where none of the prescriptions grouped in this category had one prescribed antibiotic (Example of category C prescription: Appendix 5).
- Highest relative frequency of 76.4% (42 out of 142) of prescriptions with single antibiotics was recorded for category F prescriptions followed by 68.2% for category A2, 49.1% for category A1, 48.2% for category D, 28.6% for category E and 22.4% category B.

- **Prescriptions with (2) prescribed antibiotics**

- Highest relative frequencies of prescriptions with two prescribed antibiotics within prescription categories were seen with categories E (57.1%) and D (41.4%) prescriptions where antibiotics were prescribed for prophylaxis.
- Lowest category relative frequency of 21.8% of the prescription types were seen for prescription category F where antibiotics were prescribed for conditions non-indicative for antibiotics.

- In the grouping of antibiotic prescriptions given for the treatment of diagnosed infections, prescriptions with (2) prescribed antibiotics were seen at percentage frequencies of 38.2% for A1, 27.3% for A2 and 27.3% for B prescriptions

Table 4.1.13 Percentage frequency distribution of prescriptions by categories and according to number of prescribed antibiotics per prescription

Prescription categories	Frequency of prescriptions according to number of antibiotics prescribed per prescription											
	Single antibiotic prescribed		2 antibiotics prescribed		3 antibiotics prescribed		4 antibiotics		> 4 antibiotics prescribed		Total	
	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
Prescription category A1	27	49.1 (19.0)	21	38.2 (20.8)	5	9.1 (10.2%	2	3.6 (10.5)	0	0.0 (0.0)	55	100
Prescription category A2	30	68.2 (21.0)	12	27.3 (11.9)	2	4.5 (4.1)	0	0.0 (0.0)	0	0.0 (0.0)	44	100
Prescription category B	22	22.4 (15.5)	28	28.6 ((27.7)	32	32.7 (65.3)	14	14.3 (73.7)	2	2.0 (100)	98	100
Prescription category C	0	0.0 (0.0)	0	0.0 (0.0)	3	75.0 (6.1)	1	25.0 (5.3)	0	0.0 (0.0)	4	100
Prescription category D	13	44.8 (9.2)	12	41.4 (11.9)	4	13.8 (8.2)	0	0.0 (0.0)	0	0.0 (0.0)	29	100
Prescription category E	8	28.6 (5.6)	16	57.1 (15.8)	2	7.1 (4.1)	2	7.1 (10.5)	0	0.0 (0.0)	28	100
Prescription category F	42	76.4 (29.6)	12	21.8 (11.9)	1	1.8 (2.0)	0	0.0 (0.0)	0	0.0 (0.0)	55	100
Total	142	44.3 (100)	101	32.9 (100)	49	16.0 (100)	19	6.2 (100)	2	0.65 (100)	307	100

Notation: n% values in parenthesis based on column totals
n% values without parenthesis based on row totals

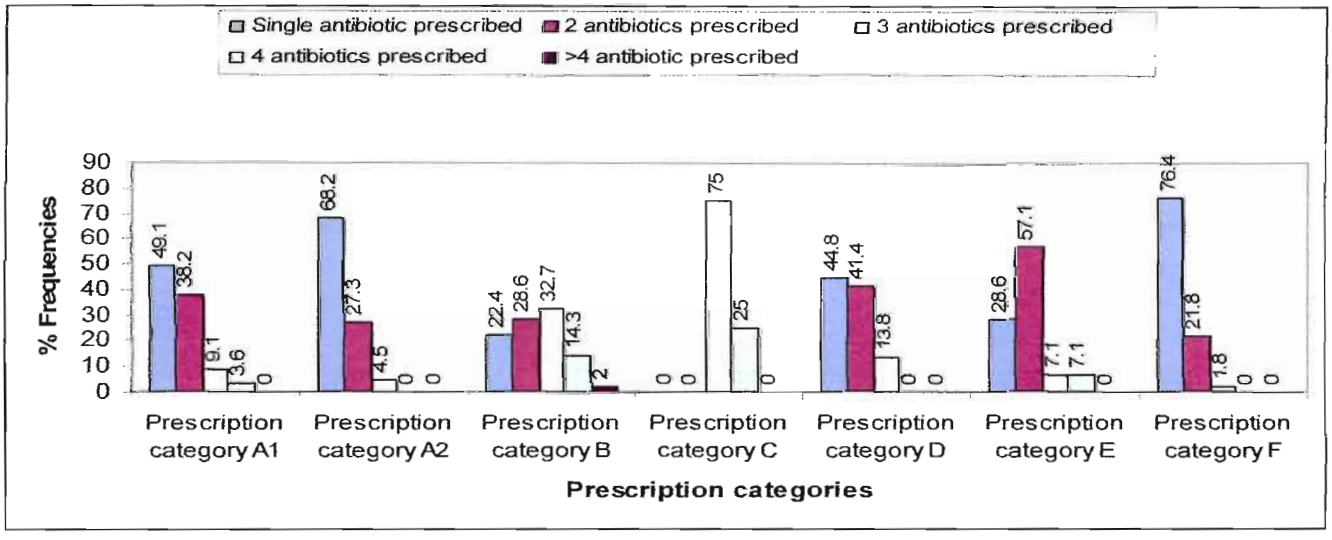

Figure 4.1.5 Percentage frequency distributions of numbers of prescribed antibiotics per prescription within prescription categories

- **Prescriptions with three (3) prescribed antibiotics**

° In the grouping of antibiotic prescriptions given empirically for the treatment of infections, prescriptions with three prescribed antibiotics were seen at percentage frequencies of 32.7% within category B, 9.1% within category A1, 4.5% within category A2 and 1.8% within category F.

° In the alternative grouping of prescriptions given for prophylaxis, prescriptions with three (3) prescribed antibiotics were also observed at respective relative frequencies of 3.8% and 7.1% for prescriptions categorised as D and E.

° Of the four prescriptions classified in category C, three contained three antibiotics prescribed per prescription

- **Prescriptions with four (4) prescribed antibiotics**

° Prescriptions with four antibiotics were prescribed within prescriptions classified in categories E, B, and F at respective group relative frequencies of 17.1%, 14.3%, and 1.8% and in groupings of prescriptions considered inappropriately prescribed for prophylaxis or treatment of infections or for cases non-indicative for antibiotic use.

° One prescription of the four prescriptions classified in category C was a prescription that contained four prescribed antibiotics.

- **Prescriptions with four more than (4) prescribed antibiotics**

° Of all assessed prescriptions for inpatients two were seen with more than four antibiotics prescribed per prescription. Both of them were classified in category B.

♦ **Effects of single and multiple antibiotic therapies on antibiotic treatment outcomes**

Tables 4.1.11.1 through 4.1.11.4 document calculated treatment success and relative treatment success rates (RTSR) of patients treated with antibiotic prescriptions with given numbers of antibiotics in categories of prescriptions patient groups were treated with.

Prescription category A1

- For patients treated with category A1 antibiotic prescriptions, the highest relative treatment success rate of 1.2 was recorded for patients treated with four antibiotics prescribed per prescription. It was followed by 0.96 for patients treated with prescriptions with two prescribed antibiotics, 0.94 for those treated with three antibiotics and 0.91 for those treated with one prescribed antibiotic per prescription.
- The lowest and highest RTSR were notably associated with patients treated with the least (one) and most (four)] numbers of antibiotics per prescription, suggesting a general trend of increasing RTSR with increasing numbers of antibiotics per prescription in the category of patients treated with category A1 prescriptions.
- Higher RTSR are demonstrated in patients treated with two antibiotics per prescription in the group as compared with lower such rates observed in patients treated with three (3) antibiotics per prescription.
- In contrast to the suggested associations of increasing RTSR with increasing numbers of antibiotics per prescription as indicated by RTSR of patient subgroups treated with one and four antibiotics per prescription, the higher RTSR demonstrated in subgroups of patients treated with two antibiotics per prescription in comparison with those treated with three antibiotics per prescription rather suggests that treatment response may not necessarily depend on the number of antibiotics prescribed per prescription in the category of patients treated with category A1 prescriptions.

Prescription category A2

- Only one patient in the group of patients treated with prescription category A2 was treated with three (3) antibiotics and determined relative treatment success rate of 1.26 for patients treated with the number of antibiotics in the group is considered statistically invalid for result evaluations to determine a trend in relative treatment success rate determinations for patients treated with antibiotic prescription in this category.
- Determined RTSR of subgroups of patients treated with prescriptions with one (1) and two (2) antibiotics in the prescription category were respectively 1.0 and 0.98.
- Lower and higher RTSR of patients treated with antibiotic prescriptions with two (2) and one (1) antibiotics per prescription as observed for patients treated with

Prescription category A1, denotes a finding in which response of patients treated with prescription category A2 were not seen to necessarily depend on numbers of antibiotics prescribed per prescription.

Prescription category B

- The highest and lowest RTSR of 1.14 and 0.75 were obtained respectively for patients treated with prescriptions with three and four or greater than four prescribed antibiotics in this prescription category.
- Subgroups of patients treated with prescriptions with two and one prescribed antibiotics demonstrated RTSR of 0.93 and 0.83 respectively.
- Calculated RTSR for subgroups of patients treated with antibiotic prescriptions with one, two, three antibiotics show a trend of increasing responses to antibiotic treatment with increasing numbers of antibiotics in patients treated with prescription category B.
- Decreases and not corresponding increases in treatment response rates were seen with patients treated with four or more antibiotics per prescription in the group of patients treated with prescription category B.

Prescription category C

All three patients and one patient treated with prescriptions with three and four antibiotics per prescription in this category of prescriptions respectively showed 100% recovery, demonstrating RTSR of 1.0 each in the subgroup of patients treated with the respective numbers of antibiotics.

- **Statistical correlations of numbers of prescribed antibiotics with treatment outcomes**

- Average number of antibiotics used in treating patients who improved, did not improve or who died were 2.11, 2.14 and 1.75.
- The effect size for differences between means of number of antibiotics used in treating groups of patients who improved or did not improve or between groups of patients who improved or who died were respectively 0.03 and 0.33.

Table 4.1.14.1 Treatment success rates of patients in prescription category groupings receiving given number of antibiotics: **PRESCRIPTION CATEGORY A1**

Number of antibiotics per prescription	Number of patients receiving prescription (excluding deaths)	Frequency distribution of prescriptions by treatment response		Treatment success rate	Relative Treatment success rate
		Improved	Not improved		
		n	n		
1	24	21	3	77.8	0.91
2	17	14	3	82.4	0.96
3	5	4	1	80	0.94
= or> 4	2	2	0	100	1.2
Total	48	41	7		
Prescription category treatment success rate: 85.4					

Table 4.1.14.2 Treatment success rates of patients in prescription category groupings receiving given number of antibiotics: **PRESCRIPTION CATEGORY A2**

Number of antibiotics per prescription	Number of patients receiving prescription (excluding deaths)	Frequency distribution of prescriptions by treatment response		Treatment success rate	Relative Treatment success rate
		Improved	Not improved		
		n	n		
1	24	19	5	79.2	1.00
2	9	7	2	77.8	0.98
3	1	1	0	100	1.26
= or >4	0	0	0	0	0
Total	34	27	7		
Prescription category therapeutic success rate : 79.4					

Table 4.1.14.3 Treatment success rates of patients in prescription category groupings receiving given number of antibiotics: **PRESCRIPTION CATEGORY B**

Number of antibiotics per prescription	Number of patients receiving prescription (excluding deaths)	Frequency distribution of prescriptions by treatment response		Treatment success rate	Relative Treatment success rate
		Improved	Not improved		
		n	n		
1	12	7	5	58.3	0.83
2	26	18	7	69.2	0.93
3	27	23	4	85.2	1.14
= or >4	16	9	7	56.25	0.75
Total	81	57	23		
Prescription category therapeutic success rate : 70.4					

Table 4.1.14.4 Treatment success rates of patients in prescription category groupings receiving given number of antibiotics: **PRESCRIPTION CATEGORY C**

Number of antibiotics per prescription	Number of patients receiving prescription	Frequency distribution of prescriptions by treatment response		Treatment success rate	Relative Treatment success rate
		Improved	Not improved		
		n	n		
1	0	0	0		
2	0	0	0		
3	3	3	0	100	1.00
= or >4	1	1	0	100	1.00
Total	4	4	0		
Prescription category therapeutic success rate :100					

- The effect size for differences between means of number of antibiotics used in treating groups of patients who did not improve or who died similarly was determined to be 0.32.

4.1.1.3.2 Results Evaluation and Discussion

- **Multiple antibiotic prescribing: A view on its appropriateness *versus* the extent of their prescribing**

Multiple antibiotic prescribing in the empiric treatment of infections is commonly seen in medical practice (Chambers, 2001: 1169). Obvious reasons prescribers give to justify such prescriptions is their desire to cover all bacterial pathogens that might be implicated in the infections they treat for better treatment outcomes. Chambers (2001:1169) expressed reservations about appropriateness of this mode of antibiotic prescribing when he indicated that prescriber's frequent use of antibiotic combinations or antibiotics with the broadest spectrum in treating infections is a cover for their diagnostic imprecision. He pointed out as further support for his reservations towards multiple prescribing of antibiotics that prescribers' selections of antibiotics are more of habit than for specific indications justifying their prescriptions of antibiotics this way. Multiple prescribing of antibiotics in the authors' opinion is inappropriate. This stand of the author may not be entirely correct. In mixed infections where bacterial pathogens with varied morphological and sensitivity characteristics are implicated multiple antibiotic prescribing may be the only means of effecting a radical cure. Stamm (2005:1719) recommended for example the use of ampicillin plus gentamicin in the treatment of complicated or upper urinary tract infections in men and women where *E. coli, Proteus, Klebsiella, Pseudomonas, Serratia, enterococci,* and *staphylococci* are suspect pathogens.

Prescribers, as findings of investigations of the extent of multiple antibiotic prescribing at study site hospitals had established, were observed generally to be inclined towards prescribing single or limited numbers of antibiotics in the empiric treatment of infections. This may be seen as promoting rational use of antibiotics in accordance with Chambers's (2001:1169) opinion about the use of fewer antibiotics in treating infections, Prescribed this way and to be seen to therapeutically effective, antibiotics must be judiciously selected with respect to their abilities to successfully eradicate bacterial pathogens implicated in infections.

Antibiotics are prescribed for the treatment of infections for reasons of their ability to act on and terminate pathogenic activities of bacteria on host cells and their usefulness and efficacy are seen to depend on how ably they do this. Different bacteria are known to be aetiological agents of given infections. Skin and soft tissue infections for example may be caused by both gram-positive and gram-negative bacteria (Ohl & Pollack, 2005:890-893; Russo, 2005: 881; Musher, 2005: 826 & 827) while for meningitis *S. pneumoniae*, *Haemophilus influenzae, Neisseria meningitidis* and *Escherichia coli* are important aetiologic agents (Elliot *et al.*, 2004:34; Musher, 2005:810; Russo, 2005: 881). For the empiric prescription of one or two antibiotics or what could be termed "small number" of antibiotics) to be seen as appropriate in treating effectively any of these exemplified infections, and for that matter any infection with multiple bacteria as possible aetiologic agents, a prescriber must be sure in the first instance of his or her selected antibiotic or few antibiotics being active against all pathogens commonly associated with the infection. This, in principle, calls for the prescribers' display of good knowledge in bacteriology of said infections and degrees of activities of antibiotics to be able to prescribe an antibiotic or few antibiotics to effectively treat such infections. Results of the section of this study which investigated prescribers' knowledge in the bacteriology of infections and principles of antibiotic prescribing (Section 4.3.5) showed significant lack of this knowledge among prescribers at all study sites. This puts into doubt whether the one or two antibiotics seen to be prescribed most commonly in treating infections are selected judiciously enough to be effective in treating these infections.

Results as indicated in Table 4.1.13 showed the majority 29.6% and 21.0% of total prescriptions with single prescribed antibiotics as respectively belonging to prescription categories A2 and F. Comparably 19% of prescriptions with single prescribed antibiotic were category A1 prescriptions. As results presentation in Table 4.1.13 further showed, as many as 76.4% and 21.8% of total prescriptions categorised as F were prescriptions with one and two prescribed antibiotics while for prescription category A2, 68.2% and 27.3% of total prescriptions were prescriptions for one and two antibiotics. By comparison, a lower 49.19% and a higher 38.2% of total prescriptions were seen as prescriptions with one and two antibiotics in te case of prescription category A1.

Prescription categories A1, A2 and F as defined in Table 3.1, were prescriptions in which antibiotics were prescribed respectively for absolute and possible bacterial infections and for clinical conditions in which bacteria infections were not considered

aetiologies. By comparing the percentage frequencies of prescriptions with one and two antibiotics classified into these prescription categories as shown, it can be inferred that prescribers gave single antibiotics mostly in situations where they tend to have doubts in bacterial infections being aetiologies of cases they treat. The observed larger relative frequencies of total antibiotic prescriptions assessed for study site hospital inpatient departments being prescriptions for one or two antibiotics may not, for this reason, be regarded necessarily as an indication of prescribers' rational prescribing of the drugs.

Though not investigated, severity of infections is speculated as more of a factor determining numbers of antibiotics prescribers use in treating infections among inpatients than a display of knowledge in judicious antibiotic selection and use. This is inferred from the relatively high tendencies of a smaller number of antibiotics per prescription used in treating infections being associated with the smaller district hospitals (Berea, Maluti, Motebang and Scott) in comparison with the higher number of antibiotics per prescription used at the Queen II hospital to which severe cases are referred from other hospitals for management. Apart from the highest frequency of prescriptions with triply prescribed antibiotics being obtained from this hospital, the only cases in which more than four antibiotics were prescribed per prescription were also seen at this hospital (Table 4.1.12). Substantiation of this speculation is further provided by results of outpatient prescription assessments where as high as 82.0% of the total numbers of prescriptions assessed were prescriptions with singly prescribed antibiotics (Section 4.1.2.3; Table 4.1.28). Infections treated in outpatient departments are characteristically not as severe as those seen in inpatient settings. Recommendations by medical speciality guidelines in the USA for patients with community acquired pneumonia who are defined as low risk patients based on a pneumonia severity index (PSI) as stated by (Labarere *et al.*(2007:480), substantiate this statement. .

The criteria combinations used in the assessment of prescriptions did not link multiple antibiotic therapies to the determination of appropriateness of antibiotic prescriptions. This is reflected in all antibiotic prescription categories defined as being appropriately or inappropriately written containing prescription combinations of single and multiple antibiotics per prescription.

- **Multiplicity of antibiotic prescribing and antibiotic treatment outcomes**

Assessment of prescription categories to establish the effect of the utilisation of multiple antibiotics produced results that generally did not show convincing links between patients' recovery from infections and the number of antibiotics they have been treated with. This has been shown from evaluations of established trends of relative treatment success rates among patient groups treated with prescriptions with varying numbers of antibiotics per prescription in categories of prescriptions classified as A1 and A2 (Tables 4.1.14.1 and 4.1.14.2). Patients' response to antibiotic treatment by these evaluations was not shown to necessarily depend on the number of prescribed antibiotics per prescription. The observed trend in relative treatment success rates among patients treated with category B prescriptions indicated similar findings. Patients treated with this category of antibiotic prescriptions showed increases in treatment success rates with lower numbers of antibiotics per prescription varying from one to three. This trend however was obliterated with treatments with higher numbers of four or more antibiotics per prescription. Decreases in treatment response rates were seen with patients treated with these higher numbers of antibiotics. Based on these results, particularly in the findings associated with patients treated with category A1 prescriptions where highest and lowest relative treatment success rates were observed for patients treated respectively with prescriptions with four and one antibiotics per prescription, it can be inferred that the number of antibiotics empirically used in treating infections can possibly have a positive impact on treatment outcomes if antibiotics are appropriately prescribed and for clinical conditions in which bacterial infections are absolute aetiologies. The number of antibiotics prescribed generally depends on the type of infection as they may be appropriate for some infections and inappropriate for others. In empiric treatment of infections, therapeutic benefits of multiple use of antibiotics may be obliterated in the event of inappropriate prescribing of the agents. This was seen in the case of patients treated with prescription category B in this study.

The relatively small number of four prescriptions with three and four prescribed antibiotics classified in category C and assessed for their effectiveness was deemed too small for substantive conclusions to be made on patients' response to number of antibiotics they were treated with in this prescription category (Table 4.1.14.1). In spite of this observation and based on the finding of 100% recovery of patients treated with the antibiotic category grouping, a predictive conclusion can be drawn to indicate that

prescribing antibiotics according to results of culture sensitivity tests has a good chance of producing positive treatment outcomes. In addition, the number of antibiotics prescribed concurrently by this observation, may only count in producing positive treatment outcomes provided such antibiotics are prescribed on the basis of their unique display of activities against bacterial pathogens implicated in the infection.

- **Inferences from statistical correlations:**

Results of effect size determinations show no practically significant differences between means of the number of antibiotics used in treating a group of patients who died or improved on one hand or a group of patients who died or did not improve on the other hand (d-values <0.5). Similarly no practically significant differences were seen in effect sizes for means of the number of antibiotics used in treating patient groups who improved or did not improve with antibiotic treatments (d-values <0.5). It can be inferred from these results that the number of antibiotics used in treating infections does not have any positive impact on treatment outcomes. It confirms results obtained from analysis of data by methods of relative frequency determinations in groups of patients treated with prescription categories A1, A2, and B to determine effects of using multiple antibiotics in treating infections which, as indicated above, established no convincing links between patients' response to antibiotic treatment and the number of antibiotics used in treating infections.

4.1.1.4 Determining leading infections and antibiotics most commonly prescribed for them at study site inpatient departments

Results of investigations to determine leading infections and antibiotics most commonly prescribed for them at inpatient departments are presented and discussed in this section. Diagnoses or symptoms indicated by prescribers have been grouped together as infections of given anatomical sites and analysed for their epidemiological trends at study sites and associations with antibiotics commonly prescribed for their treatment. Results are presented to demonstrate these patterns and compared with results of other sections of the study.

- **Determining frequencies of prescribed antibiotics: Points of note**

In determining frequencies of presentations of infections and of prescribed antibiotics as shown in Tables 4.1.14 and 4.1.15 (inpatient data) and 4.1.30 and 4.1.31 (outpatient data) the following were taken into consideration during analysis of data.

- **Patients diagnosed with multiple infections:**

  Multiple infections diagnosed concurrently were taken as separate infections and counted as such for the determinations of their prevalence at study sites over the study period. Two separate infections would be indicated for a patient diagnosed for example with respiratory tract infections concurrent with skin and soft tissue infections. With this approach the total number of patients treated would be less than the total number of infections treated.

- **Frequencies of prescribed antibiotics for given infections:**

  In retrospective drug utilisation studies it is difficult determining prevalence (frequencies) of prescribed antibiotics in treating patients diagnosed with multiple infections if the prescriber did not indicate which antibiotic was prescribed for which infection. In generating frequency tables from data compiled for these determinations a statistical program will count each prescribed antibiotic as being prescribed for each of the concurrently diagnosed infections. This will produce results in which certain infections will have certain antibiotics wrongly counted in their favour as being prescribed for them. With this as a noted limitation the following are stated as principles followed in determining frequencies of prescribed antibiotics for diagnosed infections.

  - Where one antibiotic was prescribed for multiple infections, the one prescribed antibiotic was considered as prescribed for each of the diagnosed infections and counted as such.
  - Where multiple antibiotics were prescribed for one diagnosed infection, each antibiotic was considered as prescribed individually and counted as such for the one diagnosed infection.
  - Where multiple antibiotics were prescribed for concurrently diagnosed infections each prescribed antibiotic was taken as prescribed for each of the diagnosed infections and counted as such.

- In situations of prescribed antibiotics not being commonly indicated for all infections diagnosed concurrently, the researcher still did consider each antibiotic as being prescribed for each diagnosed infection and counted them as such. This was done for as long as the prescriber did not indicate which antibiotic was prescribed for which infection and the researcher had no means of differentiating which antibiotic was prescribed for which infection. Patient Record no. 195 (Berea) is cited as an example to illustrate the situation. The patient in this record was diagnosed for respiratory tract infection (RTI) and skin and soft tissue infection (SSI) and was prescribed ampicillin, co-trimoxazole and cloxacillin. Cloxacillin is commonly indicated for staphylococcal skin infections and might be prescribed for this purpose for this patient. A prescriber could also prescribe the antibiotic in respiratory tract infections if he or she staphylococci as implicated in the infection as causative agents. Patient record no 151 (Motebang) actually exemplified a case for which cloxacillin was prescribed as a sole antibiotic in treating respiratory tract infection. In view of this and in the absence of the prescriber indicating which of the two infections for which the antibiotic was prescribed, the researcher did consider it as being prescribed for the two concurrently diagnosed infections and counted them as such. Ampicillin and co-trimoxazole were each counted similarly as prescribed for either diagnosed infection separately.

- The impact of this limitation on the results of the study is discussed in Section 4.1.1.4.2.

4.1.1.4.1 Results

Prescriber indicated diagnoses of clinical conditions suggesting infections of various anatomical sites or symptoms/symptom complexes or clinical conditions they stated as indicating presence or potential sources of infections to justify their prescription of antibiotics are listed in Table 4.1.15. Diagnosed clinical conditions non–indicative of bacterial infections for which antibiotics were prescribed either when they present singly or in combination with infections are similarly listed in Table 4.1.16. Relative frequencies of diagnosis and treatment of indicated infection types at various study sites are listed in Table 4.1.17 while percentage frequency distributions of all cases seen and treated for infections at study sites are shown in Figure 4.1.5.

Table 4.1.15 List of prescriber indicated diagnosed infections or symptoms/ symptom complexes indicating presence of infections or conditions indicating potential sources for infections at various body sites for which antibiotics were prescribed (**Source: Patient case notes**).

Respiratory tract	**Gastrointestinal tract/Abdominal cavity**	**Genitourinary tract infections**	**Skin and soft tissue**	**Bones**	**Central nervous system**	**Blood**	**Pyrexia (No specific site)**
Bronchitis; Chest pain; Cough; Cough with coloured sputum; Cough with blood stained sputum; Ear ache; Emphysema; Haemothorax; Laryngitis; Lower respiratory tract infection; Otitis media, Otitis externa; Pneumocystis carini pneumonia; Pleural effusion; Pneumonia; Pneumonia; Pneumothorax; Pulmonary fibrosis; Respiratory tract infection; Shallow breathing/Shortness of breath/dyspnoea; Silicosis; Sinusitis; Sore throat; TB; TB peritonitis; Tonsilitis; Upper respiratory tract infection(URTI)	Abdominal pain; Anal fistulae; Anal sores; Appendicitis; Dental abscess; Dental/Mouth infections Diarrhoea Gastritis Gastroenteritis Gastrointestinal infection Gingivitis Peptic ulcer disease Perianal ulcers Perineal ulcers Periondontitis Peritonitis	Abortion Genital swelling Genital ulcers Genitourinary tract infection Incomplete abortion (non septic) Orchitis Pelvic inflammatory disease Penile discharge Pyelonephritis Septic genital ulcers Septic incomplete abortion Urinary incontinence Urinary retention Urinary tract infection (UTI) Vaginal discharge Vaginal fistulas Vaginal lesions Vaginitis	Abscess; Acne; Animal bites; Bedsores; Burns (clean); Burns (septic); Caesarian surgical wound Cellulitis; Chalazia; Clamydial conjunctivitis Decubitus ulcers; Dental injuries; Diabetic foot; Eye infections; Furuncles; Gangrene; Gunshot or stab wounds (abdominal); Gunshot or stab wounds (non abdominal); Impetigo; Insect bites; Lacerations or bruises; Laparatomy Leprosy; Lesions; Panniculitis; Pustules; Scabies; Seborrhoea; Septic genital ulcers; Septic ulcers; Skin rashes; Surgical wounds (non infected); Swellings;	Fracture with prosthetic substitution; Fracture with open wound; Fracture with open wound (Septic); Osteomyelitis.	Meningitis(no indication of type) Meningitis (Bacterial) Meningitis (Cryptococcus) Head injury	Septicaemia; Systemic gonorrhoeal infection.	Enteric fever (Typhoid) Fever Chills Fever of unknown origin

Table 4.1.16 List of prescriber's indicated diagnoses or symptoms/ symptom complexes for which antibiotics were either prescribed alone or in combination with symptoms or diagnosed cases of infections (**Source: Patient case notes**).

Non infectious Conditions
Allergy; Allergic rhinitis; Anaemia; Asthma; Ascites; Arthritis; Acute renal failure; Bronchospasm; Backache; Broncho carcinoma; Bleeding superficial); Blood after urinating; Body pains; Cough (dry or colourless sputum); Common cold; Dizziness; Cor-pulmonale; Pancreatitis; Prostate cancer; Congestive cardiac failure; Cold feet; Chicken pox; Cerebrovascular accident; Dislocation; Dermatitis; Diabetes mellitus; Depression; Epilepsy/Convulsions; Eczema; Eclampsia/Preclampsia; Epistaxis; Encephalopathy; Fracture; Fungal dermatitis; Fungal infection; Influenza; Fibroid in uterus; Headache; Haemolysis; Haemorrhoids; Hypoglycaemia 2^{o} to DM; Hyperglycaemia 2^{o} to DM; Hyperacidity; Hodgkins lymphoma; Hypertension; Herpes zoster; Herpes simplex; Lymphadenopathy; Malarial prophylaxis; Neck pain; Oral thrush; Pain in the anus; Pain in the breast; Pain in the foot/ankle; Pain in the shoulder; Psychosis; Paraplegia/Hemiparesis; Genital itches; Paedal oedema of unknown cause; Immuno-compromised patient; Intestinal occlusion; Kwashiorkor; Loss of Appetite; Liver cirrhosis; Loss of weight; Mumps; Nasal congestion; Night sweats; Retrosternal Epigastric pain; Rape; Sciatica; Sneezing; Swollen eyes; Skin patches; Skin itches; Stevens Johnson Syndrome; Tooth ache; Threatened abortion; Vomiting; Vaginal bleeding; Vaginal candidiasis; Viral infections; Warts; Yellow urine;

- **Epidemiology of diagnosed infections**

As shown in Table 4.1.15, prescribers used various terms to indicate their diagnoses of infections at various anatomical sites of the body. For this study, these were taken to include respiratory tract, gastrointestinal tract and abdominal cavity, genitourinary tract, skin and soft tissue, bone, central nervous system and blood infections. Fevers or pyrexia not associated with infections of any specific anatomical site and which prescribers treat as infections of their own have been noted as diagnosis prescribers treat with antibiotics.

- **Frequency distributions of prescriber diagnosed infections: All sites**

Table 4.1.17 shows the percentage frequency distribution of variously diagnosed infection types among inpatients at study sites. Figure 4.1.6 shows frequency distributions of diagnosed infection types relative to all other clinical conditions seen and treated with antibiotics at all study sites irrespective of whether or not they were indicative of bacterial infections.

Of all cases for which antibiotic prescriptions were given as shown in Figure 4.1.6,

- 83.7% (n = 297) were diagnosed as indicative of bacterial infections as against 16.3% (n = 58) that were not;
- 29.3%, representing 35.0% (104 out of 297) of total cases diagnosed as infections, were **respiratory tract infections (RTI);**
- 24.3% (n = 88), representing 29.6% (88 out of 297) of total cases diagnosed as infections, were **skin and soft tissue infections**;
- 11.8% (n = 42), representing 14.1% (42 out of 297) of total cases diagnosed as infections, were **gastrointestinal tract (GIT)/abdominal cavity infections**;
- 10.1% (n = 36), representing 12.1% (36 out of 297) of total cases diagnosed as infections were **genitourinary tract infections (GUTI);**
- 3.4% (n = 12), representing 4.0 (12 out of 297) of total cases diagnosed as infections, were **central nervous system infections**;
- 2.0% (n = 7), representing 2.4% (7 out of 297) of total cases diagnosed as infections, were **bone infections;**
- 1.4% (n = 5) representing 1.7% (5 out of 297) of total cases diagnosed as infections, were **blood infections**;

- 0.8% (n = 3) representing 1.0% (3 out of 297) of total cases diagnosed as infections, were cases of **pyrexia** or **fevers of unknown origin**).

Table 4.1.17 Percentage frequency distribution of diagnosis and treatment of infection types among inpatients at study sites

Infection type	Frequencies of diagnosis and treatment of infection types by study sites											
	Berea		Maluti		Motebang		Queen II		Scott		Total	
	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
Respiratory tract infections	15	48.4 (14.3)	12	26.8 (11.4)	29	33.7 (27.6)	36	35.0 (34.3)	13	37.1 (12.4)	105	35.0 (100)
Gastrointestinal tract infections	1	3.2 (2.4)	10	24.4 (23.8)	10	11.6 (23.8)	12	11.7 (28.7)	9	25.7 (21.4)	42	14.1 (100)
Genitourinary infections	4	12.9 (10)	7	17.1 (19.4)	8	9.3 (22.2)	10	9.7 (27.8)	7	20.0 (19.4)	36	12.1 (100)
Skin and soft tissue infections	7	22.6 (7.9)	10	24.4 (11.4)	36	41.9 (40.9)	32	31.0 (36.4)	3	8.6 (3.4)	88	29.6 (100)
Bone infections	0	0.0 (0.0)	1	2.4 (14.3)	1	1.2 (14.3)	4	3.9 (571)	1	2.9 (14.3)	7	2.4 (100)
Central nervous system infections	3	9.7 (25.5)	0	0.0 (0.0)	2	2.3 (16.7)	6	5.8 (50.5)	1	2.9 (8.3)	12	4.0 (100)
Blood infections	1	3.4 (20.0)	1	2.4 (20.0)	0	0.0 (0.0)	2	1.9 (40.0)	1	2.9 (20.0)	5	1.7 (100)
Pyrexia or fevers with unknown origin (POU)	0	0.0 (0.0)	1	4.9 (50.0)	0	0.0 0.0	1	1.0 (50.0)	0	0.0 (0.0)	2	1.0 (100)
Sub totals (Cases of infections)	**31**	**100**	**42**	**100**	**86**	**100**	**103**	**100**	**35**	**100**	**297**	**100 (83.7)**
Diagnoses non-indicative of bacterial infections	5	19.4 (8.6)	1	2.3 (1.7)	13	15.7 (22.4)	35	29.9 (60.3)	4	16.7 (6.9)	58	16.3 (100)
Total	36	100	43	100	99	100	138	100	39	100	355	100

Notations:
- n% value in bracket determinations based on row totals
- n% value **not** in bracket determinations based on column totals
- PUO: Cases diagnosed as such by prescriber or cases diagnosed as fever without indications of any other diagnoses or signs and symptoms of infection
- Diagnoses non-indicative of bacterial infections: Diagnosed non-infectious cases for which antibiotics were prescribed in absence of concurrent infections.

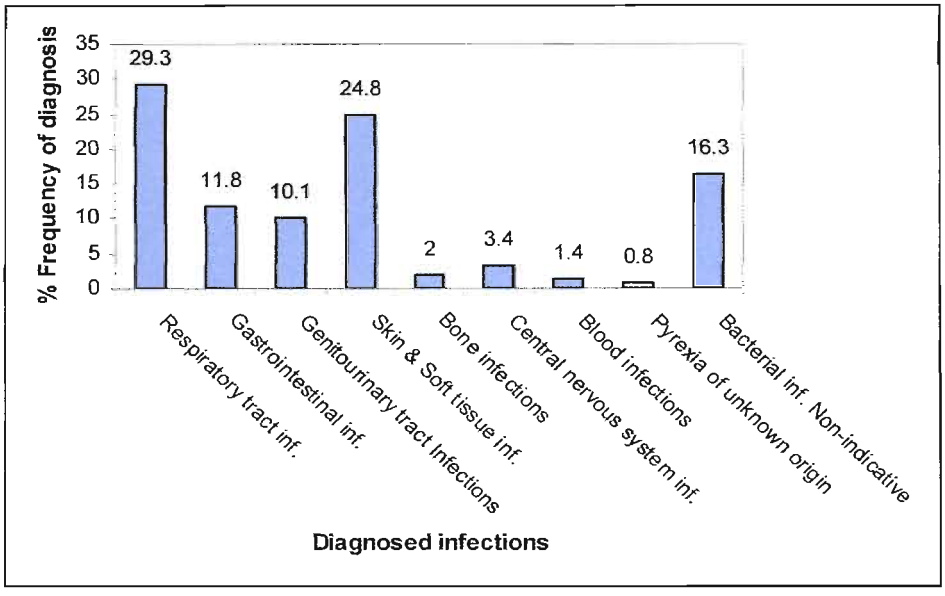

Figure 4.1.6 *Percentage frequencies of diagnosed infections treated at inpatient settings at all study sites*

- **Percentage frequencies of presentations of infection types at study site hospitals**

Percentage frequency distribution of diagnoses and treatment of infection types among inpatients at individual study sites are shown in Table 4.1.17 and outlined as follows:

- **Respiratory tract infections**

Of the total number of cases of respiratory tract infections diagnosed and treated at all study site inpatient departments (n = 105), a majority 34.3% were seen at the Queen II hospital. Similar rates of diagnosis and treatment of the infection at other study sites hospitals were 27.6% for Motebang hospital, 14.3% for Berea hospital, 12.4% for Scott hospital and 11.4% for Maluti hospital.

- **Skin and soft tissue infections**

- The total number of cases of skin and soft tissue infections encountered at all study site hospitals was 88. Of this total, 40.9% was seen at the Motebang hospital,

36.4% at the Queen II hospital, 11.4% at the Maluti hospital, 7.9% at Berea hospital and 3.4% at Scott hospital.

- **Gastrointestinal tract/Abdominal infections**

  Forty two (42) cases of gastrointestinal tract/abdominal infections were encountered at all study hospitals. Of this total 28.7% were seen and treated at the Queen II, 23.8% each at the Maluti and Motebang hospitals and 21.4% and 2.4% respectively at the at the Scott and Berea hospitals.

- **Genitourinary tract infections**

  - Genitourinary tract infections (n = 36) presented at all study site hospitals at nearly the same relative frequency. It was diagnosed at frequency rates of 27.8% at Queen II hospital, 22.2% at Motebang hospital, 19.4% each at the Maluti and Scott hospitals and 10.0% at the Berea hospital.

- **Bone, Central nervous system and Blood infections and Pyrexia of unknown origin**

  - Of the seven (7) cases of **bone infections** seen at study sites four (4) were diagnosed and treated at the Queen II hospital and one (1) each at the Maluti, Motebang and Scott hospitals.
  - Six (6) out of total twelve (12) cases of **central nervous system infections** diagnosed and treated at all study site hospitals each came from Queen II hospital, three (3) from Berea hospital and the rest two (2) and one (1) from the Motebang and Scott hospitals. No infections of the central nervous system were diagnosed and treated at the Maluti hospital during the period of study.
  - Five (5) cases of **blood infections** were reportedly seen during the study period. Of these five, two were diagnosed and treated at the Queen II hospital and one (1) each presented at the Berea, Maluti and Scott hospitals.
  - Two (2) cases diagnosed as **pyrexia of unknown origin** were respectively seen and treated at the Maluti and Queen II hospitals

- **Clinical conditions considered non-indicative of bacterial aetiologies**

° Clinical conditions considered non-indicative of bacterial infections but for which antibiotics were prescribed as Table 4.1.17 further showed represented 16.3% of all cases treated with antibiotics. Of this number 60.3% were treated with antibiotics at the Queen II hospital.

° Comparatively lower percentage proportions of 22.4%, 8.6%, 6.9% and 1.7% were treated at the Motebang, Berea, Scott and Maluti hospitals respectively.

♦ **Antibiotics most commonly prescribed at study site inpatient departments**

- **Relative frequencies of prescribing given antibiotics in wards**

Among all routinely prescribed antibiotics as Figure 4.1.6 shows, **ampicillin**, at a 26.0%, rate of prescribing of was seen as the most commonly prescribed antibiotic at all study sites. It was followed in that order by **metronidazole** (15.6%), **cloxacillin** (11.7%), **co-trimoxazole** (10.9%), **gentamicin** (10.2%), **penicillin** (6.7%), **cefotaxime** (5.0%), **erythromycin** (3.8%), **chloramphenicol** (2.6%), **ciprofloxacin** (2.3%), **nitrofurantoin** (0.9%), **ceftriaxone** (0.7%), **tetracycline** (0.4%), and **doxycycline** (0.3%). **Amikacin** and **nalidixic acid** had not been prescribed during the period of study.

- **Rates of prescribing antibiotics administered for indicated categories of infections in inpatient departments.**

Rates at which individual antibiotics were prescribed in the treatment of diagnosed infections are shown in Table 4.1.18. The extent to which individual antibiotics were prescribed for indicated infections among inpatients as determined from results documentations in the table were as outlined below.

° **Ampicillin**, the most commonly prescribed antibiotic as noted above was prescribed for all infections but mostly for *respiratory tract infections*. Its rate of prescribing for this infection relative to other antibiotics was 36.0%. For other infections it was prescribed at rates of 23.0% for *skin and soft tissue infections*, 9.0% for *genitourinary tract infections*, 6.7% for *gastrointestinal tract infections*, 3.4% for blood infections, 2.2% for bone infections and 1.8% and 0.6% respectively for *central nervous system* and *pyrexia of unknown origin.*

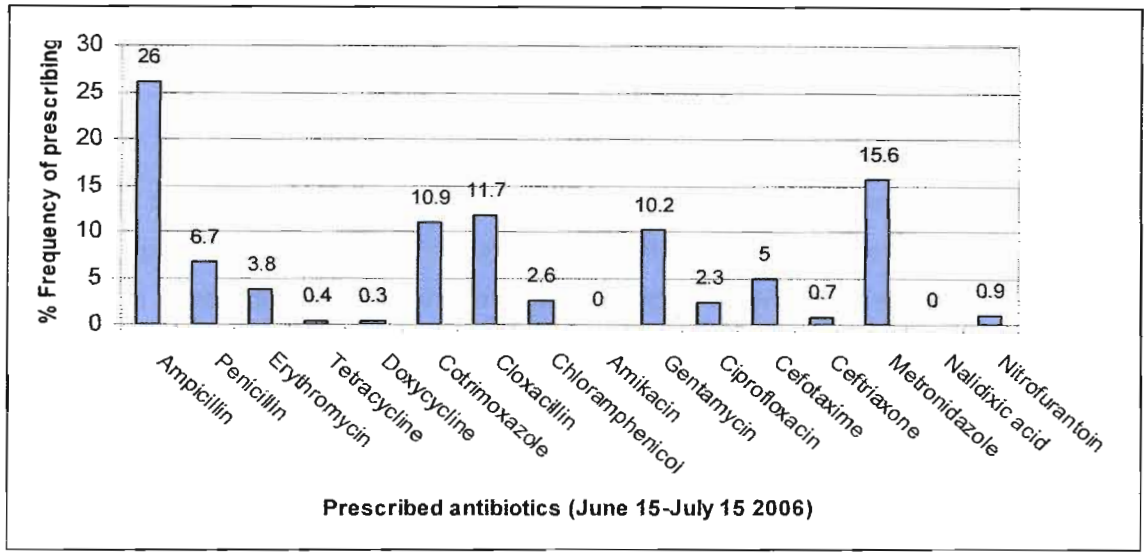

Figure 4.1.7 Percentage frequencies of prescribed antibiotics in inpatient departments within study period (June 15 -July 15 2006)

- **Metronidazole** the second commonest prescribed antibacterial agent following ampicillin was also observed to be prescribed for all types of infections except for pyrexia of unknown origin. With a rate of prescribing of 34.6% it was seen to be prescribed mostly for *skin and soft tissue infections*. It was also prescribed at a comparatively high rate of 22.4% in *gastrointestinal or abdominal infections* and at equal rates of 12.1% in *respiratory tract infections* and *genitourinary tract infections* and 11.2% in *genitourinary tract infections*.

- **Cloxacillin,** ranking third among the most commonly prescribed antibiotics at all study sites, was prescribed mainly for *skin and soft tissue infections* and at a frequency of 60.2%. It was also seen to be prescribed to a lesser extent and at respective frequencies of 6.3% for *bone infections* and 4.8% for *genitourinary* tract infections and 3.6% each for *respiratory* and *gastrointestinal tract* or abdominal infections.

- **Co-trimoxazole**, placed fourth as the most commonly prescribed antibiotic at all study sites. It was prescribed mainly for *respiratory* and *gastrointestinal tract infection*. Its rates of prescribing for these infections were respectively 46.7% and

25.3%. At respective prescribing rates of 6.3% and 3.2%, the antibacterial agent was also observed to be prescribed to a lesser extent for *skin and soft tissue infections* and *genitourinary tract infections.*

Gentamicin ranking as the fifth commonest prescribed antibiotic at study site hospitals was prescribed for all infections encountered in inpatient settings except in cases of pyrexia of unknown origin. It was prescribed mostly in cases of *skin and soft tissue* and *respiratory tract infections.* Its rates of prescribing for the two infections were respectively 28.6% and 25.7%. It was prescribed to a lesser extent and at respective rates of 15.7% for *genitourinary tract infections,* 5.8% for *gastrointestinal tract or abdominal infections*, 5.7% for *central nervous system* and 4.3% each for bone and blood infections.

- **Penicillin,** the sixth most commonly prescribed antibiotic at study site inpatient settings, was prescribed mainly for infections of the *respiratory tract* and *skin and soft tissue.* For these infections the antibiotic was respectively prescribed at rates of rates of 42.2% and 15.6%. To a lesser extent it was prescribed at rates of 11.1% for *central nervous system infections*, 8.9% for genitourinary tact infections and 2.2% for *gastrointestinal infections.* It was neither prescribed for bone and blood infections nor in pyrexia of unknown origin.

- **Cefotaxime and ceftriaxone,** considered together as the the only third generation cephalosporins (TGCs) prescribed at study sites, ranked as the seventh most commonly prescribed antibiotics at study sites and as such can be considered as less frequently prescribed antibiotics. Cefotaxime, the more prescribed of the two TGCs, was prescribed mainly for *respiratory tract* and *skin and soft tissue infections* and at equal rates of 29.4%. Comparatively, the antibiotic was prescribed at lower rates of 17.6% and 5.9% respectively for *gastrointestinal or abdominal* and *genitourinary tract infections.* Ceftriaxone was prescribed once each time in *genitourinary tract* and *central nervous system infections.*

- Prescribed at rates less than 4.0% relative to other antibiotics, **erythromycin, ciprofloxacin, chloramphenicol, tetracycline, doxycycline, nitrofurantoin, amikacin and nalidixic acid** in that order can be considered the least prescribed

Table 4.1.18 Percentage frequency distribution of prescribed antibiotics according to clinical conditions -**ALL RECORDS (INPATIENT DEPARTMENT**

Diagnosis	Frequencies of prescribed antibiotics according to clinical conditions																	
	Ampicillin/ Amoxycillin		Penicillin		Erythromycin		Tetracycline		Doxycycline		Co-trimoxazole		Cloxacillin		Chloram-phenicol		Amikacin	
	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
Respiratory tract infections	64	36.0 (34.2)	19	42.2 (10.2)	15	57.7 (8.0)	1	33.3 (0.5)	0	0.0 (0.0)	35	46.7 (18.7)	3	3.6 (1.6)	4	22.2 (2.1)	0	0.0 (0.0)
Gastrointestinal tract infections	12	6.7 (16.2)	1	2.2 1.4)	0	0.0 (0.0)	1	33.3 (1.4)	0	0.0 (0.0)	19	25.3 (25.7)	3	3.6 (4.1)	1	5.6 (1.4)	0	0.0 (0.0)
Genitourinary infections	16	9.0 (21.3)	4	8.9 (5.3)	5	19.2 (6.7)	1	33.3 (1.3)	2	100 (2.7)	3	4.0 (4.0)	4	4.8 (5.3)	2	11.1 (2.7)	0	0.0 (0.0)
Skin & soft tissue infections	41	23.0 (19.7)	7	15.6 (3.4)	5	19.2 (2.4)	0	0.0 (0.0)	0	0.0 (0.0)	6	8.0 (2.9)	50	60.2 (24.0)	5	27.8 (2.4)	0	0.0 (0.0)
Bone infections	4	2.2 (16.7)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	5	6.0 (20.8)	0	0.0 (0.0)	0	0.0 (0.0)
CNS infections	3	1.8 (11.5)	5	11.1 (19.2)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	3	4.0 (11.5)	0	0.0 (0.0)	3	16.7 (11.5)	0	0.0 (0.0)
Blood infections	6	3.4 (37.5)	1	2.2 (6.3)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	1	1.3 (6.3)	1	1.2 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)
Pyrexia with unknown origin	1	0.6 (50.0)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	1	1.3 (50.0)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)
Non-bacterial aetiology	31	17.4 (40.3)	8	17.8 (10.4)	1	3.8 (1.3)	0	0.0 (0.0)	0	0.0 (0.0)	7	9.3 (9.1)	17	21.5 (22.1)	3	16.7 (3.9)	0	0.0 (0.0)
Total	**178**	**100 (26.0)**	**45**	**100 (6.7)**	**26**	**100 (3.8)**	**3**	**100 (0.4)**	**2**	**100 (0.3)**	**75**	**100 (10.9)**	**83**	**100 (11.7)**	**18**	**100 (2.6)**	**00**	**0.0 (0.0)**

Table 4.1.18 (Continued)

Diagnosis	Frequencies of prescribed antibiotics according to clinical conditions																	
	Gentamicin		Ciprofloxacin		Cefotaxime		Ceftriaxone		Metronidazole		Nalidixic acid		Nitrofurantoin		**Total**			
	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%		
Respiratory tract infections	18	25.7 (9.6)	4	25.0 (2.1)	10	29.4 (5.3)	1	20.0 (0.5)	13	12.1 (7.0)	0	0.0 (0.0)	0	0.0 (0.0)	**187**	**27.1 (100)**		
Gastrointestinal tract infections	6	8.6 (8.1)	0	0.0 (0.0)	6	17.6 (8.1)	1	20.0 (1.4)	24	22.4 (32.4)	0	0.0 (0.0)	0	0.0 (0.0)	**74**	**10.7 (100)**		
Genitourinary infections	11	15.7 (14.7)	6	37.5 (8.0)	2	5.9 (2.7)	1	20.0 (1.3)	13	12.1 (17.3)	0	0.0 (0.0)	5	71.4 (6.7)	**75**	**10.9 (100)**		
Skin and soft tissue infections	20	28.6 (9.6)	6	37.5 (2.9)	10	29.4 (4.8)	0	0.0 (0.0)	37	34.6 (17.8)	0	0.0 (0.0)	1	14.3 (0.0)	**208**	**30.2 (100)**		
Bone infections	3	4.3 (12.5)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	12	11.2 (50)	0	0.0 (0.0)	0	0.0 (0.0)	**24**	**3.5 (100)**		
CNS infections	4	5.7 (15.4)	0	0.0 (0.0)	4	11.8 (15.4)	2	40 (7.7)	2	1.9 (7.7)	0	0.0 (0.0)	0	0.0 (0.0)	**26**	**3.8 (100)**		
Blood infections	3	4.3 (18.8)	0	0.0 (0.0)	1	2.9 (6.3)	0	0.0 (0.0)	3	2.8 (18.8)	0	0.0 (0.0)	0	0.0 (0.0)	**16**	**2.3 (100)**		
Pyrexias with unknown origin	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	**2**	**0.3 (100)**		
Non-bacterial aetiology	5	7.1 (6.5)	0	0.0 (0.0)	1	2.9 (1.3)	0	0.0 (0.0)	3	2.8 (3.9)	0	0.0 (0.0)	1	14.3 (1.3)	**77**	**11.2 (100)**		
Total	**70**	**100 (10.2)**	**16**	**100 (2.3)**	**34**	**100 (5.0)**	**5**	**100 (0.7)**	**107**	**100 (15.6)**	**0**	**0.0 (0.0)**	**7**	**100 (0.9)**	**689**	**100 (100)**		

Notations: n% value in bracket determinations based on row totals
n% value **not** in bracket determinations based on column totals

antibiotics for inpatients at study site hospitals. **Erythromycin** among the group was prescribed mainly in *respiratory tract infections.* It was prescribed at a frequency of 57.7% for this infection and also at much lower rates of 19.2% each, for *genitourinary tract* and *skin and soft tissue infections.*

- **Ciprofloxacin,** for the few times of its prescribing for inpatients was observed to be restricted to the treatment of *genitourinary tract*, *skin and soft tissue* and *respiratory tract infections.* For these cases the antibiotic was prescribed at respective frequencies of 37.5% each for *genitourinary tract* and *skin and soft tissue* infections and 25.0% for *respiratory tract infections.* It was not prescribed for all other such infections encountered among inpatients as bone, central nervous system and blood infections or pyrexia of unknown origin. By these results, ciprofloxacin is considered one of the least routinely used antibiotics at study site hospitals

Chloramphenicol was prescribed for all major infections. For the few times that it was used, the antibiotic was prescribed at rates of 27.8%, 22.2% and 16.7% in the treatment of *skin and soft tissue infections, respiratory tract infections* and *central nervous system infections.* For *genitourinary* and *gastrointestinal* tract or abdominal *infections*, the antibiotic was also prescribed at respective but lower rates of 11.1% and 5.6%.Chloramphenicol was neither seen to be prescribed for bone and blood infections nor in cases of pyrexia of unknown origin.

- **Doxycycline and nitrofurantoin** were prescribed only in cases of genitourinary tract infections for the few times that they were prescribed. For the three times that it was prescribed, tetracycline was prescribed once for the treatment of respiratory and genitourinary tract and skin and soft tissue infections.

- **Amikacin and nalidixic acid** were not prescribed for any infection during the study period.

- **Antibiotics commonly prescribed for indicated infections in inpatient departments**

From their rates of prescribing as Table 4.1.18 shows, the following are documented and listed in order of their frequencies of prescribing as antibiotics most commonly prescribed in treating indicated categories of infections among inpatients at study sites.

- **Respiratory tract infections**

  Ampicillin, with a 34.2% rate of prescribing, was found to be the most frequently prescribed antibiotic for the empiric treatment of respiratory tract infections among inpatients. It was followed in order of decreasing frequencies of prescribing by co-trimoxazole (18.7%), penicillin (10.2%) gentamicin (9.6%), erythromycin (8.0%), metronidazole (7.0%), cefotaxime (5.3%), ciprofloxacin (2.1%), chloramphenicol (2.1%), cloxacillin (1.6%) and tetracycline (0.5%). Doxycycline, amikacin, nalidixic acid and nitrofurantoin were not prescribed for the respiratory tract infections during the period of study.

- **Gastrointestinal infections**

  Prescribed at a frequency of 32.4% metronidazole was seen as the most frequently prescribed antibiotic for gastrointestinal infections. Following it in order of decreasing frequencies of prescribing for the infection were co-trimoxazole (25.3%), ampicillin (16.2%), cefotaxime, erythromycin and gentamicin (8.1%), and chloramphenicol penicillin, and cloxacillin (1.4%). Erythromycin, tetracycline, doxycycline, amikacin, ciprofloxacin, nalidixic acid and nitrofurantoin were not observed to be prescribed for the infection during the period of study.

- **Genitourinary tract infections**

  Antibiotics most commonly prescribed in genitourinary tract infections in order of decreasing frequencies included ampicillin (21.3%), metronidazole (17.3%), gentamicin (14.7%) ciprofloxacin (8.0%), erythromycin and nitrofurantoin (6.7%), penicillin and cloxacillin (5.3%), co-trimoxazole (4.0%), cefotaxime, chloramphenicol and doxycycline (2.7%), ceftriaxone and tetracycline (1.3%). Amikacin and nalidixic acid were not prescribed for the infection during the period of study.

- **Skin and soft tissue infections**

  At rates of prescribing of 24.0%, 19.7% and 17.8%, cloxacillin ampicillin, and metronidazole were respectively observed as the most frequently prescribed antibiotics for skin and soft tissue infections. Other prescribed antibiotics for the infection in order of decreasing frequencies of prescribing included gentamicin (9.6%), cefotaxime (4.8%), penicillin (3.4%), ciprofloxacin and co-trimoxazole (2.9%), erythromycin (2.4%) and chloramphenicol (2.4%) Antibiotics not seen to have been prescribed for the infection during the period of study included tetracycline, doxycycline, amikacin, and nalidixic acid.

- **Bone, central nervous system, blood infections and pyrexia of unknown origin**

  Antibiotics prescribed for rarer encountered infections together with their frequencies of prescribing as noted above included and for bone infections, metronidazole (50.0%), cloxacillin 20.8%, ampicillin (16.7%), gentamicin (12.5%); for central nervous system infections, penicillin (19.2%), cefotaxime and gentamicin (15.4%), ampicillin, co-trimoxazole and chloramphenicol (11.5%) and metronidazole and ceftriaxone (7.7%); and for blood infections, ampicillin (37.5%), gentamicin and metronidazole 18.8%. For pyrexia of unknown origin, ampicillin and co-trimoxazole were both prescribed once each time for both infections.

- **Clinical conditions non-indicative of bacterial infections**

  In the exception of amikacin and nitrofurantoin which were not prescribed for any infection during the study period all other antibiotics were reportedly prescribed for clinical conditions for which antibiotic prescriptions were not justified. The most commonly prescribed antibiotic in conditions of such sorts was ampicillin, having been prescribed at the highest frequency of 40.3%. It was followed in that order as determined by their frequencies of prescribing by cloxacillin (22.1%), penicillin (10.4%), co-trimoxazole (9.1%), metronidazole and, chloramphenicol (3.9%), and cefotaxime, nitrofurantoin, and erythromycin (1.3% each).

4.1.1.4.2 Results Evaluation and Discussion

Result presentations outlined above document in that order *respiratory tract infections*, *skin and soft tissue infections*, *gastrointestinal tract infections* and *genitourinary tract infections* as the most prevalent and hence leading infections for which antibiotics were mostly prescribed for inpatients in the five hospitals selected for this study. Other infections seen and treated, though not in the same proportions as noted leading infections also include in order of frequencies at which they are diagnosed, *central nervous system*, *blood* and *bone infections* and also *pyrexia of unknown origin*. On the basis of criteria used in selecting study site hospitals (Section 1.5.2) these results by extrapolation were assumed to be representative of the country's situation and hence would constitute areas of primary focus in infection management in Lesotho as far as principled selection and use of antibiotics are concerned.

Bacterial pathogens commonly associated with these infections and their sensitivity patterns to antibiotics currently used in the country have been investigated in Phase II of this study (Section 4.2.2). Results from this phase of the study have been taken into perspective as antibiotics commonly used in treating these infections with regard to their effectiveness based on local patterns of pathogen antibiotic sensitivities are discussed.

- **Epidemiological trends of leading infections**

Frequency distribution patterns of the respective types of infections as encountered did not show one in which these infections were seen more at the Queen II than other study site hospitals as one would expect on account of the size of this hospital and its status as a referral hospital to which severer cases from other hospitals are referred (Table 4.1.17). A most apparent reason for this is a situation of non-referral of cases of infections by other hospitals to the Queen II hospital, most probably for reasons of these other hospitals being equally capable of managing infections they encounter in terms of the range of antibiotics available to them. Infection type frequency and distribution patterns as observed, hence, are reflective more of the epidemiological trends or relative prevalence of infection occurrence within health service area (HSA) communities served by the respective hospitals than of any other factor of relevance. Respiratory tract infections needing admissions by this finding are seen to be more prevalent relatively

within the Queen II hospital HSA than other study site hospital HSAs. Similarly gastrointestinal and genitourinary tract infections are relatively prevalent at all HSAs to same degree while skin and soft tissue infections occur with dominant frequencies within Motebang and Queen II to hospitals. Other clinical infections occur at low frequencies at all health service areas.

- **Patterns of antibiotic prescribing**

- **Establishing the need of the use of antibiotics before their prescribing**

The percentage proportion of all clinical conditions for which antibiotics were prescribed unjustifiably was determined as 16.3% (Table 4.1.17). In principle antibiotics can be prescribed if sufficient evidence establishes presence of bacterial infections in the patient. The agents could also be prescribed if there is evidence of the patient being exposed to risks of developing infections. Prescribed for either purposes an antibiotic would be seen as prescribed for needs of treating or preventing infections. Prescribing co-trimoxazole, in the prophylaxis of *Pneumocystis carinii* pneumonia in patients with systemic lupus erythematosus (SLE) who are on immunosuppressive agents e.g. corticosteroids (Gilliland & Tsokos, 2002:191) or in patients with AIDS (Martin *et al.*, 1999:1809), provides an example of antibiotic prescribing for prophylaxis in patients exposed to risks of developing infections. Criteria used in the assessment of prescriptions, categorised prescriptions on this basis. Viewed from the perspective that antibiotics need to be prescribed after diagnostic workups have established the need of their use in line with the above principle, the noted 16.3% of all assessed prescriptions being prescriptions for cases for which the use of antibiotics were deemed unjustified is considered significant. By interpretation, this depicts a feature of antibiotic prescribing in which need for antibiotics are often not sufficiently established before they are prescribed. It indicates a lack of judicious diagnosis of presenting cases at study site hospitals before decisions on antibiotic treatments are made. Compared to CHAL hospitals from which only 8.6% of the total number of cases of unjustified antibiotic prescriptions came, prescribers' tendencies of prescribing antibiotics for the wrong reasons can be said to be more rampant in government than in CHAL hospitals. An overall 91.3% of prescriptions for which the use of antibiotics was not justified came from these hospitals and as a single hospital, Queen II contributed as high as 60.3% to this total making it the one hospital in the country where antibiotics are most frequently

prescribed for the wrong reasons (Table 4.1.17). Maluti hospital, on the contrary contributed, only 1.7% to the reported total number of unjustified antibiotic prescriptions assessed. The hospital by this result was observed as one hospital in the country where antibiotics are prescribed most of the time for established infections (Table 4.1.17)

- **Established patterns of empiric antibiotic prescribing**

Results of assessment of prescriptions for their categorisation into degrees of appropriateness to which they were written as outlined in Section 4.1.1.1 showed only 1.3% of all prescriptions assessed to be based on results of culture sensitivity tests. On the basis of this it is inferred that almost all antibiotics indicated in result presentations above were prescribed empirically and hence discussed within the context of their empirical use in treating indicated infections.

Determining frequencies of prescribed antibiotics for diagnosed infections had limitations in terms of identifying particular antibiotics that were prescribed for particular infections in situations of multiple antibiotic prescribing for concurrently diagnosed infections. As indicated in Section 4.1.1.4, this was a limitation that may compromise the validity of determined frequencies of prescribing certain antibiotics for certain infections. This was of concern particularly in instances where cloxacillin and nitrofurantoin which are respectively recommended in the treatment of skin and soft tissue infections (SSI), and urinary tract infections (UTI) were observed to be prescribed with other antibiotics in cases where these infections were diagnosed concurrently with other infections. Typical instances included

- Four cases in which cloxacillin was prescribed with other antibiotics in treating SSI diagnosed concurrently with otitis media (Patient record no. 195 (Berea), urinary retention ((Patient record no. 302 (Queen II), septicaemia (Patient record no. 303 (Queen II) and upper respiratory tract infection (RTI) (Patient record no. 111 (Motebang); and
- One case in which nitrofurantoin was prescribed with other antibiotics in a case of concurrent diagnosis of urinary tract infection (UTI) (Patient record no. 302 (Queen II).

The two antibiotics were counted as prescribed for all other infections concurrently diagnosed with infections for which their prescriptions are recommended when, most probably, they were not actually prescribed for these other infections. Such probable

wrong counts of these antibiotics against infections for which they are not indicated or recommended prescribed may lead to wrong conclusions being drawn with respect to their rates of use in treating these infections. Caution needs to be exercised for this reason in interpreting rates of prescribing these antibiotics for infections for which they are not commonly indicated as determined from the results analysis. On additional note, the very few cases of these antibiotics being observed to be prescribed with other antibiotics for treating multiple infections as reported above, are considered not significant enough to influence the overall antibiotic prescribing patterns as results of the study have established.

The extent to which individual antibiotics were prescribed for the treatment of various infections showed a stereotyped pattern of antibiotic prescribing in which the following were characteristically demonstrated:

- **Empiric prescribing of a number of antibiotics for most cases of infection but with a dominance of their prescribing in particular infections**

  Typical notations in this pattern of antibiotic prescribing included the empirical prescription of

  - **ampicillin** for all types of infections encountered among inpatients with an almost equal dominance in *respiratory and skin and soft tissue infections* (Table 4.1.18);
  - **penicillin** for all types of infections in the exception of bone and blood infections with dominance of its prescribing in *respiratory tract infections* (Table 4.1.18);
  - **co-trimoxazole** for all types of infections in the exception of bone and blood infections with dominance in *respiratory tract infections* and *gastrointestinal tract infections* (Table 4.1.18);
  - **chloramphenicol** for all types of infections in the exception of bone and blood infections with dominance in *skin and soft tissue, respiratory tract* and *central nervous system infections* (Table 4.1.18);
  - **gentamicin** for all types of infections encountered among inpatients with an almost equal dominance in *respiratory* and *skin and soft tissue infections* (Table 4.1.18);
  - **TGCs** for all types of infections but predominantly for *respiratory tract* and *skin and soft tissue infections* (Table 4.1.18); and

- **metronidazole** for all types of infections with dominance in *skin and soft tissue infections* and an appreciable degree of its prescription in *respiratory, gastrointestinal* and *genitourinary tract infections* (Table 4.1.18).

° **Empiric prescribing of a number of antibiotics only for particular infections.** Particular notations in this pattern of antibiotic prescribing included the prescription of

- **erythromycin** predominantly for *respiratory tract infections* and *also skin and soft tissue* and *urinary tract infections* (Table 4.1.18);
- **cloxacillin** predominantly for *skin and soft tissue* infections (Table 4.1.18);
- **ciprofloxacin** predominantly for *genitourinary tract* and *skin and soft tissue* infections and also respiratory tract infections (Table 4.1.18) and
- **nitrofurantoin** predominantly for genitourinary tract infections (Table 4.1.18).

° **Very rare use of certain antibiotics in treating infections.** This is exemplified by observed non-use of **amikacin** and **nalidixic acid** during the study period (Table 4.1.18).

Infections at given anatomical sites are more predisposed to be caused by specific pathogens according to Guglielmo (2008:56-1). Demonstrated by isolations of different bacterial pathogens from specimens from different sites of infections as shown by results of study Phase II (Section 4.2.2), infections at given anatomical sites can be caused by different pathogens. Taking this point into consideration, the observed pattern of antibiotic prescribing among inpatients in which certain antibiotics were prescribed predominantly in certain infection types relative to others can only be explained rationally if prescribers are presumed to prescribe antibiotics in the following manner:

- Use single antibiotics more in treating infections at anatomical sites for which prescribers appear to be conversant with the most probable implicated pathogens and their intrinsic sensitivities to prescribed antibiotics, or
- Prescribe multiple antibiotics in cases where they are not sure of what specific pathogen or group of pathogens could possibly be the causative agent or agents of given infections for which the antibiotics are prescribed.

The dominant prescription of ampicillin, co-trimoxazole, penicillin or erythromycin in treating respiratory tract infections presumes for example prescribers' associations of these infections principally with cocci organisms which are intrinsically sensitive to these antibiotics (Musher, 2005: 808, 811 & 824; Elliot *et al.*, 2004: 32). Ampicillin, co-trimoxazole and erythromycin, on the basis of their broader spectra of activities that extend to gram-negative organisms which are equally known to be implicated in respiratory tract infections among inpatients (Musher, 2005: 809; Chambers, 2001:1251), may most likely be prescribed singly in these infections. This not withstanding, the narrow spectra agents penicillin, gentamicin and metronidazole were also seen to be prescribed routinely in treating respiratory infections among inpatients. Penicillin is indicated for streptococci infections mainly (Petri, 2001:1196), gentamicin in gram-negative bacilli (GNB) infections (Chambers, 2001:1223), and metronidazole in infections by anaerobic bacteria (Tracy & Webster Jr., 2001:1107; Goldstein *et al.*, 2006:64; Panigrahi *et al.,* 2001:294). Prescribing these narrow spectrum antibiotics together suggests a practice of multiple antibiotic prescribing in respiratory tract infections in which these antibiotics are prescribed together with the assumption of covering streptococci, gram-negative and anaerobic bacteria. Prescribers by giving such combinations of antibiotics may be seen as presuming that these pathogens are causative agents of respiratory tract infections among inpatients.

But for the non-coverage of *Staphylococcus aureus*, prescribing these antibiotics together may be considered appropriate in treating hospital acquired lower respiratory tract infections (LRTI). According to Joshi *et al.* (1999:390) *Staphylococcus aureus* is the second most important frequent individual aetiological agent of nosocomial LRTI next to GNB which may be responsible of up to 60% of these infections. Having noted this, though, the authors acknowledged the diverse nature of aetiological agents responsible for LRTI. Bacterial pathogen associations with infections among the local population as investigated by this study also noted strong associations of *Staphylococcus aureus*, *Streptococcus pneumoniae,* non-haemolytic streptococci, *Klebsiella and E. coli* with LRTI with or without pleural effusions among inpatients (Section 4.2, Table 4.2.3). Prescribing penicillin, gentamicin and metronidazole in treating these infections is predicted to be attended with treatment failures in events of *Staphylococcus aureus* being the implicating pathogens. In view particularly of the non-coverage of this pathogen in the empiric treatment of LRTI as the above treatment regimen depicts and also the strong association *Staphylococcus*

aureus with the LRTI among the local population, it is highly recommended that the initiation of antibiotic therapy in LRTI among inpatients with the above indicated antibiotics particularly, be preceded necessarily by culture sensitivity test requests. Requests for culture sensitivity tests prior to initiation of antibiotic therapy in inpatients appear not to be regularly done at study site hospitals. This is inferred from results of inpatient prescription analysis (Table 4.1.1) and of investigations into the extent to which prescribers adhere to principles of antibiotic prescribing in inpatient settings (Section 4.3.4,.Table 4.3.20 & 4.3.24). Requests for culture sensitivity tests prior to initiation of empiric antibiotic therapy would allow for appropriate modifications to the observed antibiotic treatment regimen that seemed to be regularly used empirically in treating these infections for better management of patients for these infections.

By considerations similar to the above, the observed high rate and dominant prescribing of the semi-synthetic penicillinase resistant penicillin (SPRP), cloxacillin, in treating skin and soft tissue infections (Table 4.1.18) reflects prescribers' association of these infections more with staphylococci, than with other pathogens (Petri, 2001:1200; Lowy, 2005:821). This observation apart, the equally high rate prescribing of other β-lactamase antibiotics (ampicillin and penicillin) and of gentamicin, ciprofloxacin and metronidazole in skin and soft tissue infections (Table 4.1.18), indicates prescribers' presumptions of streptococci, gram-negative bacilli and anaerobic organisms being additional major pathogens implicated in skin and soft tissue infections among inpatients. Penicillin and ampicillin are recommended antibiotics in treating streptococcal skin infections (Wessels, 2005:825). The aminoglycosides by indications of Eliiot *et al.* (2004:53), Chambers (2001:1223) and Russo (2005:883) are recommended antibiotics for treating GNB. Tracy and Webster Jr. (2001:1107), Goldstein *et al.* (2006:64) and Panigrahi *et al.,* (2001:294) as indicated in earlier paragraghs similarly recommended metronidazole in treating anaerobic infections. The combined prescribing of penicillin and ampicillin with metronidazole or with gentamicin by these recommendations may be interpreted to suggest prescribers' assumption that skin and soft tissue infections among inpatients are equally caused by mixed infections of streptococci, anaerobic and gram-negative bacteria. This is thought to be the case particularly in light of recommendations of the combined prescription of these antibiotics in treating mixed infections of these pathogens in skin and soft tissue infections (Inglis, 2003:62). These assumptions being true, a predictive pattern of empiric antibiotic prescribing from these considerations is one in

which cloxacillin may be prescribed singly or in combination with one or more other antibiotics for purposes of covering all bacterial pathogens likely to be causative agents of these infections.

Inferring from the majority of 55.7% of assessed antibiotic prescriptions being prescriptions of multiply prescribed antibiotics (Figure 4.2), multiple antibiotic prescribing among inpatients in the manner as described for the empiric treatment of respiratory tract and skin and soft tissue infections may be holding similarly for patterns of antibiotic prescribing in the treatment of infections at other anatomical sites. To justify such patterns of antibiotic prescribing, prescribers are seen as assuming that infections at given anatomical sites are caused by all possible pathogens associated with infections at such sites. In the event of infections by single pathogens at such sites the assumption again would be that such single bacterial pathogen would be one of the possible pathogens associated with infections at the site. The presumption in such cases would be that one of the prescribed antibiotics would be the one to effect a cure hopefully. In absence of culture sensitivity test results antibiotics are presumed to be selected and prescribed in such cases based on their characteristic literature-documented intrinsic activities against different bacterial pathogens often implicated in infections among hospitalised patients. Such a manner of antibiotic prescribing appears largely not to take cognisance of local antibiotic sensitivity patterns. They are seen to have the disadvantage of either being liable to treatment failures or associated with antibiotic over-use.

- **Effectiveness predictions of prescribed antibiotics in diagnosed infections**

The ensuing discussion below views established patterns of antibiotic prescribing in different infections as diagnosed among inpatients from the perspective of what one would expect as treatment outcome predictions if the activities of prescribed antibiotics against common bacterial isolates associated with diagnosed infections are taken into consideration. Table 4.1.19 is a summary of prescriber diagnosed infections, common bacterial pathogens associated with them and antibiotics commonly prescribed for their treatment.

Though prescribed at different frequencies for indicated infections, **ampicillin, penicillin, co-trimoxazole, chloramphenicol, cloxacillin, gentamicin, TGCs,** and

metronidazole were seen to be prescribed generally for the empiric treatment of infections of the four types of infections dominantly encountered at study sites. These include *respiratory tract, skin and soft tissue, gastrointestinal* and *genitourinary tract infections*. But for its non-prescription for gastrointestinal infections, *erythromycin*, though not indicated among the first four most prescribed antibiotics for any of the infection types as shown in Table 4.1.19, was also seen to be prescribed for these infections. As explained in Section 3.5, the probability of a prescribed antibiotic being effective against bacteria isolates commonly isolated from a specimen taken from a site of infection can be determined using said isolates' sensitivities to the antibiotic and their frequencies of isolation from the specimen. This is termed "percentage overall activity" (POA) of the antibiotic against bacterial pathogens commonly implicated in the infection and is considered an important determinant of the successful use of the antibiotic in the empiric treatment of the infection. From such POA determinations of antibiotics commonly tested against bacterial pathogens most frequently isolated from specimens from sites of the infections listed in Table 4.1.19, it is possible to predict the effectiveness of commonly prescribed antibiotics in treating these infections.

Percentage overall activity determinations for various antibiotics against commonly implicated pathogens in various infections based on available culture sensitivity test results data presented in Tables 4.2.4 and 4.2.5 (Section 4.2.3) are shown in Appendices 12.i through 12.ix. **Ampicillin** by these determinations demonstrated relatively POAs of 54%, 34%, and 20% - 36% against pathogens most likely to be implicated respectively in *respiratory tract, skin and soft tissue, gastrointestinal* and *genitourinary tract infections* as listed above. Similarly, **co-trimoxazole** exhibited POAs of 41%, 34%, and 32% - 36% and **chloramphenicol** 66%, 57%, and 60% - 61%, **TGCs** 72%, 78%, and 74% - 93% and **ciprofloxacin** 85%, 81%, and 78% - 90% POAs against bacterial pathogens commonly associated respectively with these infections.

Calculated POAs of **ampicillin** and **co-trimoxazole** against pathogens commonly associated with the respective infections as indicated above, suggest the occurrence of possible high degrees of treatment failures in the empiric use of these antibiotics in treating the infections among inpatients. Considering the reported high frequencies of prescribing of these antibiotics in treating the infections (Table 4.1.18), possibilities are that empiric treatment of these infections using these antibiotics does not yield the

Table 4.1.19 Most commonly prescribed antibiotics for diagnosed infection types and common bacterial pathogens associated with them (Source: Table 4.2.3, Section 4.2.2 and Literature)

Infection type	**Commonly associated bacterial isolates implicated in infection type (Source: Table 4.2.3 & Literature)**	**FOUR or less most commonly prescribed antibiotics in order of relative frequencies of prescription in given infections (Source: Table 4.1.18)**
Respiratory tract infection	*Staphylococcus aureus, Staphylococcus epidermidis,* α-haemolytic streptococci (*S. pneumoniae*), β-haemolytic streptococci (*S. pyogenes*), non-haemolytic streptococci (Enterococci), (**Gram-positive cocci**); *Klebsiella, Escherichia coli, Haemophillus influenzae, Haemophillus parainfluenzae Pseudomonas* (**Gram-negative bacilli**) (Sputum specimen, Table 4.2.3)	Ampicillin, Co-trimoxazole, Penicillin, Gentamicin /Metronidazole
Skin and soft tissue infections	*Staphylococcus aureus, Staphylococcus epidermidis,* α-haemolytic streptococci (*S. pneumoniae*) β-haemolytic streptococci (*S. pyogenes*), non-haemolytic streptococci (Enterococci), (**Gram-positive cocci**) *Escherichia coli, Klebsiella* spp, *Proteus* spp, *Pseudomonas* spp, Acinetobacter (**Gram-negative bacilli**).Neisseria spp (**Gram-negative cocci**) Peptococcus, and Bacteroides (**Anaerobic organisms**) (Pus swab specimen, Table 4.2.3)	Ampicillin, Cloxacillin and Metronidazole, Gentamicin
Gastrointestinal infections	*Escherichia coli, Klebsiella* and *Proteus* spp, anaerobic bacteria, *Salmonella, Shigella* spp (Literature: Russo, 2005: 881-883; Keusch & Kopecko, 2005:904)	Metronidazole, Co-trimoxazole, and Ampicillin, Cefotaxime
Genitourinary tract infections	*Escherichia coli, Klebsiella* spp, *Proteus* spp, *Pseudomonas* spp (**Gram-negative bacilli**); *Staphylococcus aureus, Staphylococcus epidermidis,* α-haemolytic streptococci (*S. pneumoniae*), non-haemolytic streptococci (Enterococci), β-haemolytic streptococci (*S. pyogenes*) (**Gram-positive cocci**) (Urine specimens, High vaginal and penile, Table 4.2.3)	Ampicillin, Metronidazole, Gentamicin / Ciprofloxacin
Central nervous system infections	α-haemolytic streptococci (*S. pneumoniae*), non-haemolytic streptococci (Enterococci) *Staphylococcus epidermidis, Staphylococcus aureus* (**Gram-positive cocci**), *Neisseria spp* (**Gram-negative cocci**), *E.coli, Klebsiella, Pseudomonas, Haemophillus influenzae* (**Gram-negative bacilli**) Bacteroides (anaerobic organisms) (Cerebrospinal fluid specimen, Table 4.2.3)	Ampicillin, Penicillin, Chloramphenicol, Metronidazole
Bone infections (Osteomyelitis)	Clues taken from organisms associated with infections from which metastasis occurred. *S. aureus* and Gram-negative bacilli most commonly implicated (Literature: Parsonnet & Maguire, 2005:746 & 747).	Metronidazole, Ampicillin, Gentamicin
Blood infection (Bacteraemia)	*Staphylococcus aureus, Staphylococcus epidermidis,* non-haemolytic streptococci (Enterococci), α-haemolytic streptococci (*S. pneumoniae*) (**Gram-positive cocci**); *Proteus* spp, *Pseudomonas* spp, *Klebsiella* spp, (**Gram-negative bacilli**) (Blood specimens, Table 4.2.3)	Ampicillin, Gentamicin, Metronidazole
Pyrexia of unknown infection	*Staphylococcus aureus* Gram-negative bacilli in focal infections associated with neutropenia, HACEK group of bacteria (*Haemophillus aphrophylus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae*) if endocarditis is suspected as aetiology, *Bartonella* spp., *Legionella* spp., Coxiella burnetti, *Chlamydia psittaci* (Gelfan & Callahan, 2005: 117 &121).	Ampicillin, Co-trimoxazole

degrees of treatment outcomes prescribers expect to achieve with the established pattern of antibiotic prescribing seen and used among inpatients. This is predicted particularly if these antibiotics are singly prescribed. Comparatively, **chloramphenicol, TGCs** and **ciprofloxacin**, with their show of high degrees of activities against common bacterial isolates associated with *respiratory tract, skin and soft tissue* and *genitourinary tract infections* as their POA determinations demonstrate, are better antibiotic choices in the empiric treatment of these infections. Despite its calculated high POA against pathogens identified as commonly implicated in these infections in studied subjects and on the basis of noted limitations in this study (Section 5.6), use of **ciprofloxacin** as a single agent in the empiric treatment of these infections may result in treatment failures in cases where gram-positive cocci happen to be the sole or a part of causative agents implicated in these infections. The antibiotic is reported to have moderate activity against streptococci and is for that reason not considered an antibiotic of choice in the empiric treatment of pneumococcal pneumonia particularly (British Medical Association & Royal Society of Great Britain, 2000: 294).

In similar determinations **ampicillin**, **co-trimoxazole**, **chloramphenicol**, **TGCs** and **ciprofloxacin** were respectively shown to demonstrate POAs of 69%, 47%, 77%, 78% and 84% against pathogens commonly associated with infections of the central nervous system (Appendixes 11.i). **Ampicillin** by its show of 69% POA against pathogens commonly implicated in the infection can be used with an appreciable degree of success in treating empirically *central nervous system infections*. The high frequency rate of prescribing the antibiotic in treating the infections may in this respect be rewarding enough to merit its continuous use in the empiric treatment of these infections. This said though, the higher calculated POAs of **chloramphenicol, TGCs** and **ciprofloxacin** suggest better treatment response of *central nervous system infections* with these antibiotics. Swartz (2004:1827) in his review on bacterial meningitis indicated that for the past 15 years therapy for community bacterial meningitis has consisted of intravenous penicillin or ampicillin, TGC or both. For reasons of literature reported moderate activities of ciprofloxacin against indicated above, ciprofloxacin may not be a good choice in treating the infection if haematologic seeding by streptococci is considered an obvious cause of the infection.

Lack of data precluded determinations of POAs of other antibiotics commonly prescribed empirically in the treatment of indicated infections and also of gastrointestinal, blood, and bone infections and hence an estimation of treatment success rates likely to be achieved with the empiric use of these antibiotics in treating these infections.

Enteric gram-negative bacilli, (*Escherichia coli*, *Klebsiella* and *Proteus* spp) and anaerobic bacteria as noted in Chapter 2 are common isolates from specimens of abdominal infections including peritonitis, appendicitis and abdominal abscesses, (Russo, 2005: 881-883). Gastroenteritis demonstrating as watery diarrhoea and vomiting and other forms of intestinal infections e.g. dysentery and bloody diarrhoea are more associated with nontyphoidal *Salmonella, Shigella* spp and intestinal pathogenic *Escherichia coli* (Keusch & Kopecko, 2005:904). Based on their intrinsic antibacterial activities co-trimoxazole, aminoglycosides, β-lactamase stable penicillins, cephalosporins and the fluoroquinolones (ciprofloxacin), chloramphenicol and metronidazole in cases of abdominal infections complicated with anaerobic bacteria can, by literature recommendations, be used as antibiotics of choice in the treatment of these infections (Lesser & Miller, 2005:902; Keusch & Kopecko, 2005:905; Zhao *et al.*, 2001:156; Agha & Golberg, 2009:1). Patterns of antibiotic use in treating the infections as the study shows, demonstrate principally the use of metronidazole, co-trimoxazole and ampicillin in treating these infections in inpatient settings (Table 4.1.18). Metronidazole is indicated mainly in infections of anaerobic bacteria (Kasper, 2005:945). The dominant prescribing of the antibacterial agent over the other antibiotics in treating gastrointestinal or abdominal infections indicates the single use of the antibacterial agent in treating most cases of the infection. This, by interpretation, connotes prescribers' presumption of anaerobic bacteria being the most implicated in gastrointestinal infections even in gastroenteritis (Kasper, 2005:945; Inglis, 2003: 245). This basically is incorrect in view of the above indicated pathogens documented in the literature as being associated with gastrointestinal infections. It suggests an indiscriminate over-use of the antibacterial agent in the treatment of infections of the anatomical site. Lack of data as noted above precluded the calculation of POAs for antibiotics against pathogens that would have been commonly isolated from specimens of infections at the site and hence no means of predicting the effectiveness of prescribed antibiotics in treating the infection. This said though, low therapeutic success rates are speculated to be achieved with the observed patterns of antibiotic use in treating infections at the anatomical site.

This inferred from the rare or non-prescribing of the quinolones (ciprofloxacin and nalidixic acid) and the observed prescribing of the non-stable β-lactamase penicillins (ampicillin and penicillin) in treating gastrointestinal infections. From result presentations in Table 4.2.5, the quinolones on one hand and ampicillin and co-trimoxazole on the other hand were respectively seen to exhibit very high and very low activities against enteric pathogens noted in the literature and indicated above as being associated with gastrointestinal infections.

Bone infections, bacteraemia and infections of the central nervous systems are generally results of haematogenous seeding or contiguous spreading of pathogens from infections manifesting at other anatomical sites of the body like the respiratory, gastrointestinal, genitourinary tracts and the skin and soft tissues (Musher, 2005:810).

Osteomyelitis is known to be caused 50% of the time by *S. aureus* either from haematogenous seeding or contiguous spread from septic arthritis, though the infection from both sources can be polymicrobial involving gram-negative and anaerobic bacteria depending on the microbial flora of the infection from which infecting pathogens metastasised (Parsonnet & Maguire, 2005:746). As further noted by the authors, antibiotic therapy in principle, is commenced only after infecting pathogens have been identified. Empiric antibiotic therapy of the infection when given should include antibiotics active against *S. aureus* and gram-negative organisms where infections by these organisms are possible. Literature recommended antibiotics for empiric therapy thus include semi-synthetic penicilinase resistant penicillins e.g. cloxacillin, TGCs, aminoglycosides or fluoroquinolones (Parsonnet & Maguire, 2005:747). Viewed against the above literature on possible causative microbial agents of osteomyelitis and the recommended antibiotic therapy in the management of the infection, the non or rare prescriptions of cloxacillin and ciprofloxacin and also the high rate prescribing of ampicillin in treating the infection suggest inadequate choices of antibiotics and hence a high possibility of low therapeutic success rates being achieved in the treatment of *osteomyelitis* at study site hospital. Gram-negative bacteria which, by literature reports could be implicated in osteomyelitis (Parsonnet & Maguire, 2005:746) are reported by the findings of this study to be highly resistant to ampicillin (Table 4.2.5, Section 4.2.3.1).

Escherichia coli and *Staphylococcus aureus* are the most common clinically significant bacteria isolates from blood (Russo, 2005; Banister, 2000: 364) though bacteraemia due to other pathogens notably, *Neisseria meningitidis, Pseudomonas*, and even anaerobic bacteria are also possible (Kasper, 2005:944; Ohl & Pollack, 2005:890; Stephens *et al.*, 2005:852). Results of research Phase II established *Staphylococcus aureus* and *Escherichia coli* and other gram-negative bacteria as major isolates from bacteraemic blood in line with literature findings as noted above (Table 4.2.2, Section 4.2.2). The observed pattern of empiric antibiotic prescribing for the infection which characteristically demonstrated 37,5% rate of *ampicillin* prescribing compared with the 18.8% rates of gentamicin and metronidazole prescription, suggests single use of the antibiotic about twice the time that it may be seen prescribed together with gentamicin and metronidazole in treating bacteraemic episodes at study sites (Table 4.1.18). It further suggests more of prescribers' presumption of other pathogens, most rationally streptococci against which the antibiotic is most active (Table 4.2.4), being responsible for bacteraemia other than the literature indicated common isolates associated with the infection as indicated above. This presumption may be correct in cases where haematological seeding resulting in the bacteraemia may be coming from streptococcal infections of other sites of the body. In the event of such presumptions being incorrect as suggestive of the dominant isolations of *Streptococcus aureus* and gram-negative bacilli from blood specimens (Figure 4.2.12), one could speculate that for most of the times that ampicillin was prescribed as a single antibiotic for the empiric treatment of bacteraemia it was actually prescribed in the treatment of *Escherichia coli* and *Staphylococcus aureus* bacteraemia. Both literature and research findings document ampicillin as highly inactive against *Escherichia coli* and *Staphylococcus aureus* (Russo, 2005:882; Lowy, 2005:821) (Table 4.2.5). This predicts high treatment failure rates on occasions that treatment of the infection is effected by the use of single prescriptions of ampicillin. Ampicillin as a β-lactam antibiotic synergistically enhances the activity of gentamicin (Musher, 2005:813; Sabella & Goldfarb, 1999:3). The prescribing together of the two antibiotics for this reason, or prescribing them together with metronidazole as suggestive of the above reported pattern of antibiotic prescribing in bacteraemia, is predicted to have high treatment responses when used in treating bacteraemia with E. coli and anaerobic as causative organisms.

Pyrexia or fever of unknown origin (FUO) is a diagnostic challenge because it has many causes (Lorenze *et al.*, 2001:779). Some of these causes Gelfan and Callahan (2005:117) cited as infections, neoplasms, temporal arteritis, adult Still's disease, drug-related and factitious fever. Infections among these remain the main leading diagnosable cause of the condition and may include invariably extrapulmonary tuberculosis, prolonged mononucleosis syndromes caused by Epstein-Barr virus, cytomegalovirus, or human immunodeficiency virus (HIV). Other such recognised infections include poorly localised intraabdominal abscesses, renal, retroperitoneal and paraspinal abscesses which remain difficult to diagnose. Slow growing organisms in infective endocarditis, namely, organisms of the HACEK group (*Haemophillus aphrophylus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae*), *Bartonella* spp., *Legionella* spp., *Coxiella burnetti*, *Chlamydia psittaci* and fungi as well as prostatitis, dental abscesses, sinusitis, cholangitis and fungal diseases, notably histoplasmosis involving reticuloendothelial system, may also be infectious causes of FUO which may present with diagnostic difficulty (Gelfan & Callahan, 2005: 117; Tsakahara *et al.*, 2000:1990; Mourad *et al.*, 2003:545). Neutropenia accompanying FUO predisposes patients to focal bacterial and fungal infections, as well as bacteraemic, catheter associated, and perianal infections (Gelfan & Callahan, 2005: 121). Antibiotic therapy, if deemed necessary in FUO as, for example, in cases of nosocomial FUO use of vancomycin for coverage of methicillin resistant *Staphylococcus aureus*, as well as broad-spectrum gram-negative coverage with piperacillin/tazobactam, Ticarcillin/clavulanate, carbapenems (imipenem or meropenem) are recommended (Gelfan & Callahan, 2005: 121). In the event of concurrent manifestation of vital sign instability or neutropenia with FUO as the authors further indicated, fluoroquinolone plus piperacillin or vancomycin plus ceftazidime or cefepime or a carbapenem with or without an aminoglycoside are recommended.

Intensive diagnostic workups in conditions of FUO to identify possible sources of the condition are necessary for the choice of drugs to use, antibiotics inclusive, in effective patient management. The observed prescription of ampicillin and co-trimoxazole in light of literature-compiled information about FUO, including conditions for antibiotic use and the recommended antibiotics to be used in such cases, gave impressions of no therapeutic benefits being achieved with the use of these antibiotics. This particularly

seemed to be the case in the face of the unimpressive percentage sensitivities of bacteria isolates towards the two antibiotics as reported in Table 4.2.4, Section 4.2.3.1.

4.1.1.5 Determining patterns of antibiotic prescribing in and patients' responses to post-surgical antibiotic prophylaxis

Results of investigations into patterns of antibiotic prescribing in the prophylaxis of post-surgical infections are presented below. Antibiotics commonly used and their associations with types of surgical wounds for which they are prescribed were documented and discussed in the light of their expected and demonstrated efficacies in preventing infections of the wound types in which they were prescribed.

4.1.1.5.1 Results

Tables 4.1.20, 4.1.21 and 4.1.22 respectively show percentage frequencies of surgical wound types treated by prophylactic antibiotic administration, percentage frequency distribution of prescribed antibiotics according to surgical wound types and patients' responses to such treatments in different wound type categories.

- **Percentage frequency distributions of surgical wound types**
  - Of the number of total inpatient antibiotic prescriptions assessed for all study sites, thirty-one (31) were prescribed for purposes of preventing infections of post-surgical wounds.
  - Of the number of total surgical wound types treated two (2) out of thirty-one (31) or 6.5% were inflicted through abdominal surgical operation, 38.7% through non-abdominal surgical operations and 54.8% through caesarean operations.

- **Patterns of antibiotic prescribing in post-surgical wound prophylaxis**
  - Antibiotics prescribed either singly or in combination for post-surgical wound prophylaxis of the three indicated major surgical wound types were as outlined below:

Table 4.1.20 Frequencies of surgical wound types treated prophylactically

Surgical wound type	Frequency	
	n	n%
Abdominal surgical wound	2	6.5
Non-abdominal surgical wound	12	38.7
Caesarean surgical wound	17	54.8
Total	31	100

Table.4.1.21 Percentage frequency distribution of prescribed antibiotics/antibiotic combination according to surgical wound types

Surgical wound type	Frequencies of prescribed antibiotics									
	Ampicillin		Ampicillin +Gentamicin		Ampicillin+ Metronidazole		Ampicillin + Penicillin G		Ampicillin + Ciprofloxacin	
	n	n%	n	n%	n	n%	n	n%		
Abdominal surgical wound	0	0.0	0	0.0	2	100	0	0.0	0	0.0
Non-abdominal surgical wound	4	33.3	0	0.0	0	0.0	0	0.0	1	8.3
Caesarean Surgical wound	2	11.8	5	29.4	7	41.2	1	5.9	0	0.0
	Co-trimoxazole+ Metronidazole		Gentamicin + Metronidazole		Cloxacillin		Cloxacillin +Ampicillin		Total	
	n	n%	n	n%	n	n%	n	n%	n	n%
Abdominal surgical wound	0	0.0	0	0.0	0	0.0	0	0.0	2	100
Non-abdominal surgical wound	0	0.0	0	0.0	5	41.7	2	16.7	12	100
Caesarean surgical wound	1	5.9	1	5.9	0	0.0	0	0.0	17	100

- **Abdominal surgical wounds**

Ampicillin and **metronidazole** were prescribed in post-surgical wound prophylaxis of all two cases of abdominal surgical wounds encountered.

- **Caesarean surgical wounds**
  - Of total seventeen (17) cases of caesarean surgical wounds treated for the prevention of post-surgical infections

- **Ampicillin** was prescribed as a single antibiotic in two (2) cases representing 11.8% of the wound types treated as such;
- **Ampicillin** and **metronidazole** were prescribed in combination in seven (7) cases representing 41.2% of all such treated cases;
- **Ampicillin** and **gentamicin** were prescribed in combination in five (5) cases which also represented 29.4% of the wound types treated for prophylaxis of infections; and
- **Ampicillin** and **penicillin G, co-trimoxazole and metronidazole and gentamicin and metronidazole** were prescribed in indicated combinations in one (1) case each representing 5.9% each of the total cases of the wound types treated for post-surgical prophylaxis.

♦ **Post-surgical prophylactic wound treatment response rates**

° As Table 4.1.22 shows no patient receiving prophylactic antibiotic treatment for their surgical wounds had his or her wound becoming septic during the period of hospital stay. This gave a 100% post-surgical antibiotic therapy success rate in the category of patients to whom antibiotics were prescribed for post-surgical wound prophylaxis.

Table 4.1.22 Percentage frequency distributions of patients' responses to post-surgical antibiotic prophylaxis by surgical wound types

Surgical wound type	Number of cases treated	Average number of days spent on admission	Frequencies of patients' responses to post-surgical antibiotic prophylaxis					
			Wound septic		Wound not septic		Total	
			n	n%	n	n%	n	n%
Abdominal surgical wound	2	12	0	0.0	2	100	2	100
Non-abdominal surgical wound	12	7.9	0	0.0	12	100	12	100
Caesarean Surgical wound	17	8.2	0	0.0	17	100	17	100
Total	31	8.3±2.3	0	0.0	31	100	31	100

4.1.1.5.2 Results Evaluation and Discussion

Surgical incisions provide portals of entry into body tissues for bacterial pathogens through intact skin or mucosal barriers and thus do serve as major routes for contracting infections during surgical procedures or periods of post-surgical wound care. Surgical wounds provide environments conducive to microbial colonisation and growth and pathogens that become inoculated into such wounds during or after surgical procedures can result in infections with grave clinical concerns (Pier, 2005:700). In prevalence, surgical site infections are the second most common cause of nosocomial infections (Bratzler & Houck, 2005:595). Abscess formation normally provoked by a number of pathogens particularly anaerobic bacteria, staphylococci and streptococci, are characteristic signs of infections of surgical wounds (Piers, 2005:706). To prevent such infections it is usual practice in a therapeutic manoeuvre referred to as "surgical prophylaxis" to give antibiotics within an hour or two before surgical incision to prevent bacterial colonisation and infections of incised surgical wounds (Burke, 2001:S78; Osmon, 2000:105; Akalin, 2002:S4). Post-surgical administration of the antibiotic in such cases is discontinued after 24 hours, a time period after which no benefit with respect to the purpose of the antibiotic therapy seems to be derived (Burke, 2001:S78). Some authorities, however, do recommend such therapies to continue for 72 hours (Bratzler & Houck, 2005:397). In all surgical cases of prophylactic use of antibiotics as studied in this research no antibiotics were seen to be prescribed and used in the manner as defined within the meaning of surgical prophylaxis described above. All antibiotics were prescribed and given after surgical procedures and implied prescribers' intention to suppress post-surgical infections manifesting from bacteria colonising surgical wounds either during perioperative period or period of post-surgical care of operation wounds. Ensuing results evaluations and discussion are done in the context of post-surgical rather than preoperative or perioperative antibiotic therapy to prevent post-surgical infections.

- **Pathogen associations with surgical wound types**

Antibiotic selection for successful surgical prophylaxis or treatment of post-surgical infections is largely based on knowledge of the types and local antibiotic sensitivity patterns of bacterial pathogens likely to inoculate surgical wounds during or after surgical procedures (Polk & Christmas, 2000:105,). These normally are associated with

the site of surgical incision and in practice antibiotics selected for prophylaxis must cover the expected pathogens for that operative site (Bratzler & Houck, 2005:400; SIGN, 2008:29). Writing on antimicrobial prophylaxis in adults, Osmon (2000:105) indicated the following bacterial pathogens as associated with post-surgical infections resulting from the indicated surgical procedures. They include,

- **cardiothoracic surgery**, *Staphylococcus aureus*, coagulase negative staphylococci and Gram-negative bacilli;
- **gastrointestinal/abdominal surgery**, gram-negative bacilli and oro-pharyngeal anaerobes;
- **gynaecologic** and **obstetric procedures**, gram-negative bacilli, enterococci, group B streptococci, anaerobes;
- **head** and **neck surgery**, *Staphylococcus aureus*, streptococci and oropharyngeal anaerobes;
- **urologic procedures**, Gram-negative bacilli;
- **neurosurgery**, *Staphylococcus aureus* and coagulase negative staphylococci; and
- **ophthalmic** and **orthopaedic** procedures, *Staphylococcus aureus*, coagulase negative staphylococci, streptococci, and Gram-negative bacilli

Based on these, the selection of antibiotics to prevent post-surgical wound infections of the major surgical wound types identified at study sites should in principle target the following organisms in the cases of the indicated wound types. They include,

- **abdominal surgical wounds**, gram-negative bacilli and oro-pharyngeal anaerobes;
- **non abdominal surgical wounds**, gram-negative bacilli, *Staphylococcus aureus,* coagulase negative staphylococci and streptococci; and
- **caesarean surgical wounds**, gram-negative bacilli, enterococci, group B streptococci and anaerobic bacteria.

From literature findings on sensitivity patterns of bacterial pathogens as reported in Chapter 2 the following antibiotics are considered intrinsically active against indicated pathogens and can hence be prescribed in post-surgical prophylaxis of surgical wounds they are most liable to infect. They include:

- **Staphylococci**: the semi-synthetic penicillinase resistant penicillins (e.g. **cloxacillin** or **flucloxacillin, oxacillin** and **nafcillin,** the **cephalosporins** and the **carbapenems** (Lowy, 2005:821; Elliot *et al.*, 2004 28);
- **Anaerobic organisms (***Peptostreptococcus* spp, *Bacteroides* spp, Fusobacterium spp, *Prevotella* spp**): metronidazole, β-lactam/β-lactamase resistant antibiotic combinations** (e.g. Ampicillin/sulbactam or amoxycillin/clavulanic acid or ticarcillin/clavulanic acid or piperacillin/tazobactam) and **aminoglycosides,** and **quinolones** (Kasper, 2005:945); and
- **Gram-negative bacilli** (E*scherichia coli, Proteus, Klebsiella, Pseudomonas, Serratia, Enterobacter*): **TGCs** (Ceftriaxone and cefotaxime), **gentamicin**, ticarcillin/clavulanate or imipenem-cillastin, ciprofloxacin (Stamm 2005:1719; Elliot *et al.*, 2004:53).

- **Effectiveness predictions of patterns of antibiotic prescribing in surgical prophylaxis at study sites**

Demonstrated patterns of antibiotic prescribing in post-surgical prophylaxis in this study, showed significant dominance of prescriptions of cloxacillin and ampicillin as single or combinations of the two in surgical prophylaxis of non-abdominal surgical wounds, of ampicillin and metronidazole or ampicillin and gentamicin in caesarean surgical prophylaxis and of ampicillin and metronidazole in abdominal surgical wound prophylaxis (Table 4.1.21). Most other antibiotics like co-trimoxazole ciprofloxacin, or penicillin, though seen prescribed with ampicillin or metronidazole, are rather minimally used in this study (Table 4.1.21).

Most gram-negative bacilli which are also organisms to be covered in the prophylactic treatment of non-abdominal surgical wound types are *β-lactamase* producing and hence resistant to ampicillin (Elliot *et al.*, 2004:53). Similarly, most *Staphylococcus aureus* are *β-lactamase* producing, and are resistant to ampicillin (Lowy, 2005:821). Infections of the wound types by indications of Osmon (2000:105) are associated mainly with these pathogens. Taking the above indicated sensitivity patterns of these pathogens to ampicillin into consideration, the prescription of the antibiotic alone for post-surgical prophylaxis of infections of non-abdominal surgical wounds is thought to provide inadequate coverage of possible pathogens implicated in infections of the surgical

wound types. If the prescription of the antibiotic is assumed to be done with prescribers knowing the most likely implicated bacterial pathogens involved in infections of the wound type, it would at best be taken as indicative of their presumption of gram-positive streptococci or penicillin sensitive *Staphylococcus aureus* being the only organisms to be covered in the surgical prophylaxis of these wound types. Ampicillin demonstrates appreciable activity against these organisms as literature findings (Nguyen & Chung, 2005:1145; Inglis, 2003:21) and results of local bacterial pathogen antibiotic sensitivity determinations indicate (Section 4.2, Table 4.2.4). Its combination with cloxacillin as sole antibiotics used in the prophylaxis of the surgical wound type adds, presumably for coverage, methicillin sensitive *Staphylococcus aureus* to prescribers' list of organisms which in their opinion, are most likely to cause infections of these types of surgical wounds. This combined use of the antibiotics as sole agents in the prevention of post-surgical infection of the wound types is considered indicative of prescribers' non-consideration of gram-negative bacilli as possible aetiological agents that need to be covered in post-surgical wound infection of non-abdominal surgical wounds according to Osmon (2000:105). By indications of results of local bacterial pathogen antibiotic sensitivity patterns (Section 4.2.2, Table 4.2.5), ampicillin is seen to be largely ineffective against *β-lactamase* producing organisms including gram-negative bacilli as literature findings reported. The prescription of the antibiotic alone in surgical prophylaxis of non-abdominal surgical wounds predicts failures in the prophylactic treatment of the indicated surgical wound type. It suggests lack of knowledge on the part of prescribers in the bacteriology of non-abdominal post-surgical infections and the the extent of therapeutic usefulness of ampicillin in combating bacterial infections generally.

The use of ampicillin and metronidazole in abdominal surgical prophylaxis covers only anaerobic bacteria, the majority of which are documented in the literature to be intrinsically sensitive to the two antibacterial agents (Kasper, 2005:945), without effective coverage of gram-negative bacilli. The reported pattern of antibiotic prescribing in post-surgical prophylaxis in abdominal surgery here again questions prescribers' understanding of principles of antibiotic selection in surgical prophylaxis and expected effectiveness of the treatment.

Ampicillin and metronidazole and ampicillin and gentamicin are reportedly the two main antibiotic combinations prescribed in the prophylaxis of caesarean surgical wound

infections in this study (Table 41.18). Both drug combinations do not completely cover pathogens associated with infections of caesarean surgical wounds which, according to Osmon (2000:105), include gram-negative bacilli, enterococci, group B streptococci and anaerobes and predicts treatment failures of post-surgical infections caesarean surgical wound types in instances when the antibiotic combinations are used. Ampicillin and metronidazole may effectively prevent infections of the wound type by anaerobic bacteria as indicated above but not gram-negative bacilli against which both antibiotics are not effective (Elliot *et al.*, 2004:53; Russo, 2005:882; Tracy & Webster Jr., 2001:1106). According to Tracy and Webster Jr., (2001:1106), metronidazole by its mechanism of action is effective against only obligate anaerobes and not against gram-negative bacilli. Activity of gentamicin is directed mainly against aerobic gram-negative bacilli (Chambers, 2001:1223) and not anaerobic bacteria and its combination with ampicillin in preventing infections of caesarean surgical wounds, though synergistic against enterococci, another commonly implicated causative agent of infections of the wound types (Wessels 2005:831; Osmon 2000:105), leaves out these organisms sufficiently uncovered to cause infections of the wounds.

Ampicillin as reported in the case of antibiotic prescribing in post-surgical prophylaxis of non-abdominal wounds, was prescribed alone some of the times and also with penicillin G in cases of post-surgical prophylaxis of caesarean surgical wounds (Table 4.1.21). This pattern of antibiotic prescribing least covers pathogens with most chances of being implicated in post-surgical infections of caesarean surgical wounds as indicated above. It predicts prophylactic treatment failures of the surgical wound type and also underscores a lack of adequate knowledge on the part of prescribers in the principles of antibiotic selection in post-surgical wound prophylaxis. In a few cases only (2 out of 17) metronidazole was seen to be prescribed with gentamicin and co-trimoxazole for the prophylactic treatment of the surgical wound types (Table 4.1.21). Co-trimoxazole is intrinsically active against a wide range of bacteria including gram-positive cocci and gram-negative bacilli (Petri Jr,, 2001:1177). The combination of the antibacterial agent with gentamicin and metronidazole in the post operative prophylaxis of the surgical wound type on the basis of this is predicted to be effective preventing infections of the surgical wound types. Considering its reported low activity patterns against both Gram-positive cocci and gram-negative bacilli locally however, (Section 4.2, Table 4.2.4), the use of the antibacterial agent in surgical prophylaxis is not advised in Lesotho.

Contrary to predicted failures in responses to observed patterns of antibiotic prescribing in the prophylactic treatment of indicated surgical wound types a 100% post-surgical antibiotic prophylaxis success rate was achieved as indicated by the non-development of sepsis of the studied wounds during the average 8 ±2.3 days for which patients were hospitalised in all cases where the prescriptions were made (Table 4.1.22). In a study in which surgical patients given five days and over courses of antibiotics for post-surgical prophylaxis after their operations and were then followed for 30 days for any development of surgical-site infections, Eriksen *et al.,* (2003:15,16) showed that 28 out of 77 of such patients who developed surgical-site infections from a total 396 studied population, had their infections diagnosed in outpatient clinics 10.5 days after they had been discharged from hospital. The determined 100% post-surgical antibiotic prophylaxis success rate as observed is considered attributable more to insufficient data and insufficient time within which patients were assessed for the outcomes of their prophylactic treatments than to the effectiveness of the prescribed antibiotics in preventing surgical site infections. This is in view of the results of the study by Eriksen *et al.,* (2003:15,16) as reported, the rather small number of patients (31) seen to be treated for post-surgical prophylaxis in this research and the short number of days patients stayed in hospital on the average (8.3±2.3 days, Table 4.1.22). It is envisaged by implication, therefore, that lower than observed post-surgical antibiotic prophylaxis success rates would have been recorded if data size had been larger or if patients had been followed for their response to prophylactic treatment of their surgical wounds after their discharge from hospital.

Another probable reason, but one rather unsubstantiated by results of this study, is to attribute the observed 100% post-surgical antibiotic prophylaxis success rate to the successful employment of aseptic techniques in surgical procedures inclusive, for example, of surgical scrub, skin antisepsis and preoperative shaving and skin preparations. According to Osmon (2000:104), these as factors among others relating to operative procedures in addition to patient-related factors (age, nutritional status, diabetics, smoking status, obesity, coexisting infections at a remote site, colonisation with organisms, altered immune response) may increase the risk of surgical site infection. It is speculated, as indicated above, that rigid employment of aseptic techniques, has the potential of reducing microbial contamination of surgical wounds at

the time of surgery, would reduce the development of surgical site infections to exercise a positive impact on outcomes of post-surgical wound prophylaxis.

4.1.2 Outpatient antibiotic prescription assessment

Prescriptions analysed included all outpatient antibiotic prescriptions (N = 865) collected from outpatient departments of study site hospitals during a one-month study period dating from June 15 to July 15 2006.

4.1.2.1 Outpatient antibiotic prescribing patterns according to prescription categories, study sites and prescriber qualifications

The section outlines results of frequency distribution of prescriptions according to study sites, categories of appropriateness and prescriber qualifications. It documents the origins of assessed prescriptions, explains established patterns of appropriateness in which prescriptions are written and notes the extent to which prescriptions are appropriately or inappropriately written by respective prescribers in outpatient departments.

4.1.2.1.1 Results

- **Origin of assessed prescriptions**

Percentage frequency distribution of assessed prescriptions according to study sites and prescriber qualifications are shown in Figure 4.1.8 and Table 4.1.23. These results showed that,

- 50.0% (n = 436) of the total number of prescriptions assessed came from Queen II hospital and its affiliate clinics, 18.6% (n= 161) from Maluti hospital, 19.2% form Motebang hospital, 9.0% from Scott hospital and 3.0% from Berea hospital.
- nurse clinicians and doctors were respectively responsible for writing 13.6% and 86.4% of total 865 prescriptions assessed.

Of the total number of outpatient prescriptions assessed for individual study site hospitals, nurse clinicians and doctors were responsible respectively for writing

- 19.9% (32 out of 161) and 80.1% (129 out of 169) at Maluti hospital;
- 1.2% (2 out of 166) and 98.2% (164 out of 166) at Motebang hospital;

- 16.7% (73 out of 436) and 83.3% (363 out of 436) at Queen II hospital;
- 14.3% (11 out of 77) and 85.7% (66 out of 77) at Scott hospitals; and
- 100% (25 out of 25) of prescriptions assessed for Berea study site hospital were written by doctors.

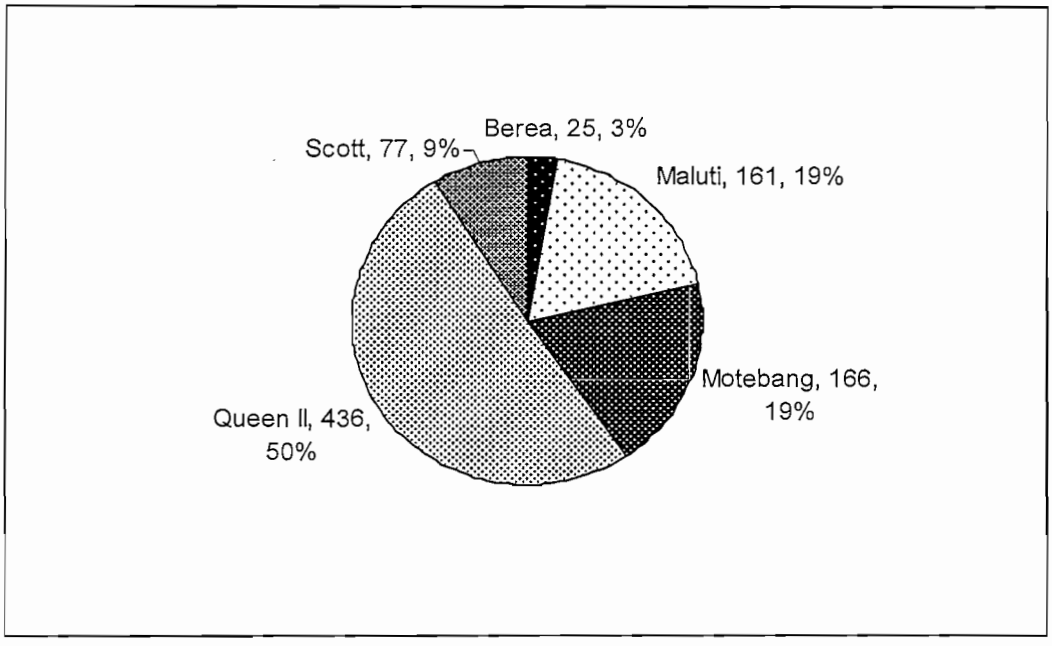

Figure 4.1.8 Percentage frequency distribution of outpatient prescriptions by study site

Table 4.1.23 Number of prescriptions according to study site and qualifications of prescribers

Study site	Frequencies of prescriptions according to prescribe qualifications				
	Doctors		Nurse Clinician		Total
	n	n%	n	n%	n
Berea	25	100	0	0.0	25
Maluti	129	80.1	32	19.9	161
Motebang	164	98.8	2	1.2	166
Queen II	363	83.3	73	16.7	436
Scott	66	85.7	11	14.3	77
Total	747	86.4	118	13.6	865

- **Prescription categorisation**

All of the 865 outpatient prescriptions studied for their appropriateness were successfully assessed and classified into seven (7) predefined prescription categories by procedures detailed in Chapter 3, Sections 3.3.2 and 3.3.4. They include, as indicated and defined in the procedures, prescription categories A1, A2, B, C, D, E, and F (Table 3.1). Of the indicated total number of prescriptions assessed as shown in Figure 4.1.8,

- category A prescriptions of which categories A1 and A2 prescriptions respectively represented 34.6% (n = 299) and 43.8% (n = 378) of the total number of prescriptions studied, constituted 78.4%
- category B prescriptions constituted 6.6%;
- no prescriptions were classified in category C, indicating no antibiotics being written in outpatient departments of study sites during period of study based on culture sensitivity test results in outpatient departments;
- prescriptions written for prevention of infections represented 2.9% of the total number of prescriptions assessed and consisted of 2.7% and 0.2% (n = 2) each of category D and category E prescriptions respectively;
- prescriptions classified in category F represented 12.1% of the total number of out patient prescriptions studied; and
- prescriptions inappropriately prescribed either for treatment of infections or for conditions in which antibiotic uses were unjustified in total represented 18.7% of the total number of antibiotic prescriptions studied.

Percentage frequency distribution of prescription categories within individual study site hospitals showing the extent to which prescriptions are written appropriately at these hospitals is further shown in Figure 4.1.9. According to indications in the figure, the following can be observed:

- Prescriptions classified in category A2 constituted 64% (16 out of 25) of all outpatient antibiotic prescriptions assessed for their appropriateness for **Berea hospital** and is followed in that order by prescription categories A1 and B with percentage frequencies of 12.0% (3 out of 25) and 8.0% (2 out of 25). No outpatient antibiotic prescriptions were classified into prescription categories D and E for the Berea hospital study site.

- Prescription category A1 similarly made up a majority 41.0% (66 out of 161) of all prescriptions assessed for **Maluti hospital** and is followed by prescription categories A2, B, D, E and F, with respective percentage frequencies of 32.3% (52 out of 161), 11.2% (18 out of 161), 4.4% (7 out of 161) and 0.6%(1 out of 161), 10.6% (7 out of 161).
- Prescription category A2 constituted a majority 48.2% (80 out of 166) of all prescriptions assessed for **Motebang hospital** followed respectively by prescription categories A1 [33.7% (56 out of 166)], F [12.1% (20 out of 166)] and B [6.0% (10 out of 166)]. No prescriptions were classified in categories D and E for this study site hospital.
- Prescription category A2 were seen at highest percentage frequency of 44.7% (195 out of 436) at the **Queen II hospital** and were followed respectively by prescription categories A1, F, B, D and E with respective percentage frequencies of 32.1% (140 out of 436), 12.8% (56 out of 436), 6.4% (28 out of 436), 3.7% (16 out of 436) and 0.23% (1 out of 436).

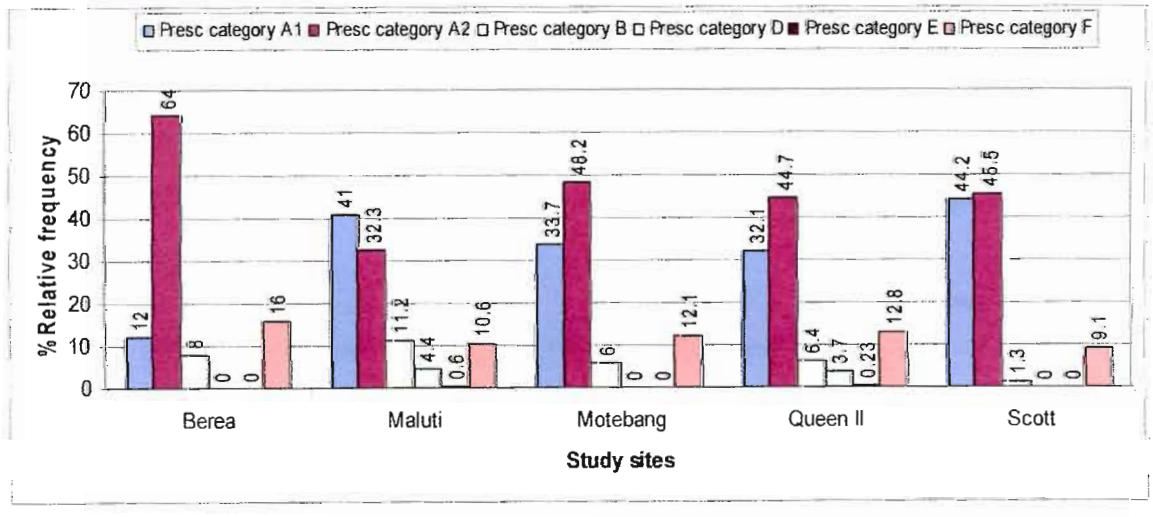

Figure 4.1.9 Frequency distribution of prescriptions according to indicated categories of appropriateness at respective study sites

- Prescription categories A1 and A2 respectively and uniquely constituted high and almost equal percentage proportions of 44.2% (34 out of 77 and 45.5% (35 out of 77) of total assessed prescriptions at **Scott hospital**. In comparison prescription categories F and B were seen at much lower percentage frequencies of 9.1% (7 out of 77) and 1.3% (1 out of 77) respectively. No prescriptions were classified in categories D and E for the study site.

◆ **Prescription categories according to prescriber qualifications**

Percentage frequency distribution of prescription categories according to prescriber qualifications at respective study sites are shown in Table 4.1.24.

- **Berea hospital**

All prescriptions assessed and classified into respective categories of appropriateness were written by doctors. The following points are noted from the percentage frequency distributions of prescription categories as observed for the hospital.

- The vast difference between percentage frequencies of category A1 (12.0%) and A2 (64.0%) prescriptions is indicative of most doctors prescribing antibiotics for clinical conditions they diagnose as possible infections instead of differentially diagnosing such conditions to establish absolute presence of bacterial aetiologies before prescribing antibiotics.
- There is a high tendency among doctors to prescribe antibiotics for cases where the use of the agents is considered unjustified (prescription category F)

- **Maluti hospital:**

Of the total number of prescriptions, 129 and 32 were written by doctors and nurse clinicians respectively. Of these 41.9% and 37.5% in that order were categorised as A1, 30.2% and 40.6% as A2, 10.9% and 12.5% as B, 4.7% and 3.1% as D and 11.6% and 6.3% as F.

- From the above percentage frequency distributions of prescription categories according to prescriber qualifications the following could be noted.

- Doctors at the study site hospital more capably identified infections with absolute bacterial aetiologies than nurse clinicians (prescription category A1).
- Nurse clinicians prescribed antibiotics more for possible infections than doctors (prescription category A2)
- Both doctors and nurse clinicians had almost equal tendencies of writing antibiotic prescriptions inappropriately (Prescription category B).
- Doctors wrote antibiotics for prophylactic reasons more than nurse clinicians (prescription categories D & E).
- Doctors write antibiotic prescriptions for unjustifiable reasons more often than nurse clinicians (Table 4.1.24).

- **Motebang hospital:**

Of the total number of 164 prescriptions written by doctors 32.9% were classified as category A1, 48.0% as A2, 6.1% as B and 12.2% as F. Two (2) prescriptions out 166 assessed for the study site hospital were written by nurse clinicians and both were classified in the prescription category of A1. It is noted from results that

- The majority of doctors prescribed antibiotics for clinical cases of which they were not sure of bacterial pathogens being aetiologies without differentially diagnosing and authenticating the presence of bacterial pathogens as aetiologies in such cases first before prescribing the agents (Table 4.1.24).

- **Queen II hospital**:

A total of 363 and 73 prescriptions were respectively prescribed by doctors and nurse clinicians at the Queen II hospital. The results in Table 4.1.24 indicated the following:

- Doctors at the hospital identify more infections with absolute bacterial aetiologies (prescription category A1) than nurse clinicians.
- Compared to doctors, nurse clinicians prescribed antibiotics more often for possible infections (prescription category A2)
- Doctors wrote antibiotics for prophylactic reasons more than did nurse clinicians (prescription categories D & E)
- Percentage of prescriptions written inappropriately (prescription category B) by doctors was higher than those written by nurse clinicians

Table 4.1.24 Prescription categories according to study sites and prescriber qualifications

Prescription categories	Frequencies of prescription categories according to study sites and prescriber qualifications															
	Berea				Maluti				Motebang				Queen II			
	Doctor		Nurse Clinician		Doctor		Nurse Clinician		Doctor		Nurse Clinician		Doctor		Nurse Clinician	
	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
A1	3	12.0	0	0.0	54	41.9	12	37.5	54	32.9	2	100	123	33.9	17	23.3
A2	16	64.0	0	0.0	39	30.2	13	40.6	80	48.8	0	0.0	152	41.9	43	58.9
B	2	8.0	0	0.0	14	10.9	4	12.5	10	6.1	0	0.0	27	7.4	1	1.4
C	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
D	0	0.0	0	0.0	6	4.7	1	3.1	0	0.0	0	0.0	16	4.4	0	0.0
E	0	0.0	0	0.0	1	0.9	0	0.0	0	0.0	0	0.0	1	0.3	0	0.0
F	4	16.0	0	0.0	15	11.6	2	6.3	20	12.2	0	0.0	44	12.1	12	16.4
Total	25	100	0	0.0	129	100	32	100	164	100	2	100	363	100	73	100
	Scott				Total											
	Doctor		Nurse Clinician		Doctor		Nurse Clinician									
	n	n%	n	n%	n	n%	n	n%								
A1	30	45.6	4	36.7	264	35.3	35	29.7								
A2	31	47.0	4	36.7	318	42.6	60	50.8								
B	1	1.5	0	0.0	54	7.2	5	4.2								
C	0	0.0	0	0.0	0	0.0	0	0.0								
D	0	0.0	0	0.0	22	2.9	1	0.9								
E	0	0.0	0	0.0	2	0.3	0	0.0								
F	4	6.1	3	27.3	87	11.6	17	14.4								
Total	66	100	11	100	747	100	118	100								

Notation: n% calculations based on column totals

- Both doctors and nurses demonstrated high propensities to prescribing antibiotics for unjustifiable reasons (prescription category F) but nurse clinicians were more prone to prescribe antibiotics this way than doctors.

- **Scott hospital:**

Of a total 66 and 11 prescriptions that were written respectively by doctors and nurse clinicians, 45.6% (30 out of 66) and 36.7% (4 out of 11) were classified as prescription category A1. Similarly, 47.0% (31 out of 66) and 36.7% (4 out of 11) were classified as prescription category A2, 1.5% (1 out of 66) and 0.0% (0 out of 11) as category B and 6.1% (4 out of 66) and 27.3% (3 out of 11) as category F.

The results revealed the following:

- Doctors at Scott hospital identified more infections with absolute bacterial aetiologies (prescription category A1) than nurse clinicians.
- Compared to nurse clinicians doctors prescribed antibiotics more often for possible infections than nurse clinicians (prescription category A2).
- Both doctors and nurse clinicians demonstrate low propensities to prescribe antibiotics inappropriately (prescription category B) for the treatment of infections.
- Compared to doctors, nurse clinicians demonstrated higher tendencies to prescribe antibiotics for unjustifiable reasons (prescription category F).

- **All study sites**

Of the total number of 747 and 118 prescriptions assessed for all study site hospitals that were written respectively by doctors and nurse clinicians, 35.3% and 29.7% were classified as prescription category A1. Forty-three per cent (42.6%) and 50.8% were classified as prescription category A2, 7.2% and 4.2% as B, 2.9% and 0.9% as D, 0.3% and 0.0% as E and 11.6% and 14.4% as F. By comparisons of percentages of total numbers of prescriptions written by doctors and nurse clinicians and classified in respective categories of appropriateness as summarised above from Table 4.1.24, the following could be noted as characteristic antibiotic prescribing behaviours of doctors and nurse clinicians at all study site hospitals:

- Doctors differentiate infections with absolute bacterial aetiologies more often from those caused by other pathogens (Prescription category A1.

- Nurse clinicians in the reverse tend to prescribe antibiotics more for infections with possible rather than absolute bacterial pathogens as aetiological agents (prescription category A2).
- Based on adherence to principles of antibiotic prescribing, doctors were seen to prescribe antibiotics more inappropriately than nurse clinicians for treatment of infections (prescription categories B).
- Doctors prescribed antibiotics for prophylactic reasons more often than did nurse clinicians (prescription category D and E).
- Compared to doctors, nurse clinicians tended to prescribe antibiotics more often for clinical conditions considered not needing antibiotic therapy (prescription category F).

4.1.2.1.2 Results Evaluation and Discussion

Origins of assessed prescriptions

Distribution patterns of assessed prescriptions as results denote are largely indicative of the sizes of study hospitals and patient populations accordingly seen. Queen II hospital with its 450 bed size and status as both a district and referral hospital situated in the capital city is the largest hospital and serves the greatest part of the country's population (Ministry of Health and Social Welfare Lesotho, 2002: 4). That 50.0% of all outpatient prescription records studied came from this hospital indicates higher patient population within the health service area (HSA) served by this hospital. Comparatively, the smaller 19.0% each of prescription records coming from the Motebang and Maluti hospitals which in that order are the second and fourth largest hospitals in the country in terms of bed sizes (Ministry of Health and Social Welfare, 2002: 4) or the 9.0% and 3.0% of such records coming from Scott and Berea hospitals suggests very low patient populations within HSAs served by these other study site hospitals.

With the observed large difference in prescription records studied at the Queen II and other study site hospitals, inclusive even of the second and fourth largest hospitals in the country as indicated, it could be assumed deductively that the patient populations seen at the Queen II hospital on a daily basis is far larger than patient populations seen and treated daily at all other hospitals in the country. With this assumption, medical practice

in Lesotho can be considered as being focused particularly within the Queen II HSA. Patterns of antibiotic prescriptions as this study established, though depictive more of patterns of antibiotic prescribing in outpatient departments at the Queen II hospital and its affiliate clinics, is largely reflective of what should be considered a "true picture" of patterns of outpatient antibiotic prescribing in the country.

Antibiotic prescribing in outpatient departments, generally, is not restricted to doctors only, though they form the major prescriber qualification category responsible for over 80% of all antibiotic prescriptions written in outpatient departments at all study sites as results of this study imply (Table 4.1.24). Except for Motebang study site hospital where they contributed to only 1.2% of prescriptions assessed and for the Berea hospital where no prescription from them were seen and assessed, nurse clinicians contributed a significant 14.3% to 19.9% (17.1% on the average) of outpatient antibiotic prescriptions studied from study site hospitals. Though they formed the minority of the two prescriber qualifications responsible for outpatient antibiotic prescriptions studied, the inclusion of prescriptions from nurse clinicians in the study enabled valid inferences to be made on degrees to which established patterns of antibiotic prescribing in outpatient departments, are attributable to both doctor and nurse prescriber qualifications.

Prescription categorisation

Analysis of results of prescription assessment of antibiotic prescriptions for study site outpatient departments showed a majority of 78.4% of these prescriptions to be written appropriately (Category A) in accordance with antibiotic prescribing principles, with up to 43.8% (prescription category A2) and 34.6% (prescription category A1) of them being written respectively for possible and absolute bacterial infections (Table 4.1.11). By interpretation these results demonstrate that the majority of prescribers adhered to principles of antibiotic prescribing as they prescribed antibiotics for infections presenting in outpatient departments. In spite of this, however, the higher percentage of category A2 than category A1 prescriptions as observed prompts an awareness of a high degree of antibiotic prescribing for suspected bacteria infections among the patient group. This in a way demonstrates inadequacy in prescribers' abilities to ascertain bacterial pathogens as aetiological agents of infections before they prescribe outpatient antibiotics for infections presenting in outpatient departments.

The low 4.2% of total prescriptions assessed being prescriptions inappropriately written for the treatment of infections (prescription category B) confirms the reported high degree of appropriate prescribing of antibiotics on the basis of prescribers' adherence to antibiotic prescribing principles. The relatively high percentage (14.4%) of prescriptions seen to be inappropriately written for clinical conditions for which antibiotic prescriptions were not justified (prescription category F) is of great concern both economically and therapeutically. This percentage of antibiotic prescriptions predicts the percentage of total antibiotics wasted on account of their being prescribed for conditions for which they are not indicated. This may translate into a significant monitory loss to health institutions and patients. It also contributes unnecessarily to antibiotic over-use which is known to promote the development of pathogens' resistance to antibiotics (and its consequent antibiotic treatment failures.

Relating prescribers' adherence to principles of antibiotic prescribing to therapeutic appropriateness of antibiotic prescriptions

To be adjudged appropriately prescribed, Gaur and English (2006:343) mentioned that antibiotics should be prescribed when they are indicated, i.e. when bacterial infections are present as aetiological agents and that they should be cost-effectively selected to provide antimicrobial coverage for the diagnosed infection. The definition of appropriate use of antibiotics by the World Health Organization (2001:15) on one other hand, placed emphasis on the cost-effective use of these drugs in ways that would maximise their clinical therapeutic effect. By these definitions, both Gaur and English (2006:343) and World Health Organization (2001:15) were seen to tie down appropriateness of antibiotic prescriptions to their correct indications for infections for which they are prescribed and their cost-effectiveness in treating such infections. Inferring from these definitions, category A2 prescriptions, cannot be considered as being appropriately prescribed since their therapeutic effectiveness cannot be contemplated for reasons of their being prescribed for infections that may or may not be present. Category A1 prescriptions on the other hand were prescribed to target specific pathogens and their therapeutic effectiveness for that reason can be predicted. They may be considered in this regard to be appropriately prescribed even by the above definitions. By these considerations, adherence to principles of antibiotic prescribing as observed may produce prescriptions that are appropriate in principle but not necessarily appropriate when their therapeutic effectiveness is considered

Comparative assessment of abilities of prescriber qualification groups in writing prescriptions of defined prescription categories

Results of data analysis showing comparative degrees to which doctors and nurse clinicians write antibiotic prescriptions appropriately at respective study sites are presented in (Table 4.1.24).

They indicate an overall pattern in which nurse clinicians were seen as more disposed than doctors to prescribing antibiotics both in infections for which bacterial pathogens may only be possible aetiologies (prescriber category A2) and in clinical conditions for which antibiotic prescriptions were not justified (prescriber category F). The following could be offered as explanations to this pattern:

- Nurse clinicians within the health care system of Lesotho are restricted to the prescription of categories of antibiotics which happened to be antibiotics commonly used in treating less serious infections. These are listed as ampicillin/ penicillin V, benzathine penicillin, benzyl penicillin, procaine penicillin, erythromycin, cloxacillin, and co-trimoxazole. (Ministry of Health & Social Welfare, 1990: 30). The restriction allows them to make appropriate selections of antibiotics for prescribing in infections they diagnose at primary health care (PHC) or health centre (HC) levels where they are assigned. Currently updated standard treatment guidelines allow treatment of genitourinary tract infections including sexually transmitted diseases, at Health centres. Nurse clinicians hence could be seen prescribing such other antibiotics as ciprofloxacin, doxycycline or tetracycline and metronidazole which are recommended for treating the infection (Ministry of Health & Social Welfare, 2006: 65).
- By their restrictions to practising at primary health care (PHC) or health centre (HC) levels, nurse clinicians may actually have been referring more serious cases of bacterial infections needing further diagnosis and treatment to doctors at hospital levels.
- Nurse clinicians possibly lack the diagnostic expertise in distinguishing bacterial infections and clinical conditions manifesting with similar symptoms.

Doctors in the alternative showed greater disposition than nurse clinicians in prescribing antibiotics for infections in which bacterial pathogens have been identified as absolute aetiologies (prescription category A1) (Table 4.1.24). In spite of this finding, doctors have also been seen to be responsible for a significant percentage proportion of antibiotic

prescriptions written for possible bacterial infections (prescription category A2) at all study sites.

In cases of inappropriate prescribing of antibiotics doctors in the overall were seen to prescribe antibiotics inappropriately more often than nurse clinicians (Table 4.1.24). These findings hold both doctors and nurse clinicians equally accountable for established patterns of antibiotic prescribing in outpatient departments in view of observed non-existence of much difference in prevalence rates of respective prescription category types written by the two prescriber qualification categories.

4.1.2.2 The impact of appropriateness of antibiotic prescribing on average costs of antibiotic prescriptions

Results of average costs of antibiotic prescriptions categorised into respective groups of appropriateness for all study sites are outlined in this section, evaluated and discussed from a perspective tended to establish associations between appropriate prescribing and costs of prescribed antibiotics.

4.1.2.2.1 Results

According to the results in Table 4.1.25 the ,

- average costs of prescriptions as determined for each prescription category classified for all study sites were R 11.18±9.90 for prescriptions classified as category A1, R7.91±15.84 for those classified as category A2, R11.02±11.41 for category B prescriptions, R7.26±4.97 for category D prescriptions, R11.28±2.28 for category E prescriptions and R7.47±6.67 for prescription category F
- No prescriptions emanating from outpatient departments were classified as belonging to category C.

Table 4.1.25: Frequency distribution of prescriptions by categories and costs according to study sites

Study site	Frequencies and costs of prescriptions by categories								
	Prescription category A1			Prescription category A2			Prescription category B		
	n	Total Cost	Average cost	n	Total Cost	Average cost	N	Total Cost	Average cost
Berea	3	18.75	6.25±4.15	16	158.72	9.92±7.4	2	16.46	8.23±8.9
Maluti	66	722.04	10.94±9.18	52	605.80	11.65±9.30	18	171.72	9.54±7.83
Motebang	56	605.36	10.81±7.19	80	575.2	7.19±6.12	10	138.10	13.81±13.70
Queen II	140	1519.00	10.85±10.87	195	1273.35	6.53±6.70	28	310.22	11.07±13.55
Scott	34	480.42	14.13±11.06	35	378.35	18.75± 46.21	1	13.58	13.58± 0.00
Total	299	3345.57	11.18±9.90	378	2991.42	7.91±15.84	59	650.08	11.02±11.41
	Prescription category D			Prescription category E			Prescription category F		
	n	Total Cost	Average cost	n	Total Cost	Average cost	n	Total Cost	Average cost
Berea	0	0.00	0.00	0	0.00	0.00	4	30.36	7.59±5.78
Maluti	7	58.1	8.30±4.87	1	9.67	9.66	17	150.79	8.87±6.43
Motebang	0	0.00	0.00	0	0.00	0.00	20	166.40	8.32±4.67
Queen II	16	108.80	6.80±5.09	1	12.88	12.88	56	351.12	6.27±6.99
Scott	0	0.00	0.00	0	0.00	0.00	7	78.68	11.249.12
Total	23	166.9	7.26±4.97	2	22.55	11.28±2.28	104	777.35	7.47±6.67

Calculated "d - values"

Formula: d-value = $(\mu_1 - \mu_2)/\sigma^*$ where μ_1 and μ_2 are mean costs of antibiotic treatment for patient groups treated with respective antibiotic prescription categories and σ^* the maximum of the two standard deviations of the two compared groups

Mean costs of prescribed antibiotic per prescription

Compared groups	d - values
A1 and A2	0.16
A1 and B	0.01
A2 and B	- 0.15

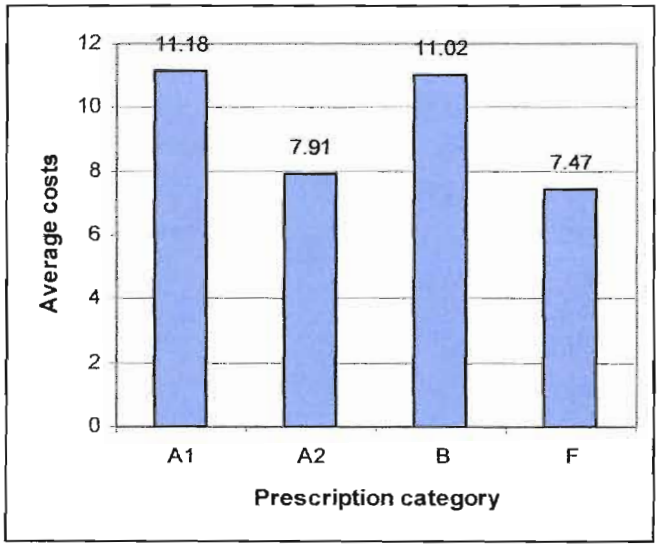

Figure 4.1.10: Frequencies of average costs of prescriptions for categories of prescriptions used for treatment

Essential notations from the above list of average costs of prescriptions constituting respective prescription categories and also from Figure 4.1.10 drawn on purpose with extracted data from Table 4.1.27 to highlight differences in average costs of prescription categories include the following:

- Average costs of antibiotic prescriptions written appropriately for the treatment of infections in which bacterial pathogens have been positively identified as causative agents (prescription category A1) were seen to be higher than those in which similar prescriptions were given for infections in which bacterial pathogens were only assumed aetiologies (prescription category A2) but almost equal to those written inappropriately for the treatment of infections (prescription category B).
- Prescriptions inappropriately written for the treatment of infections (prescription category B) were on average cost found to be more than those appropriately written for infections with possible bacterial aetiologies (Prescription category A2) and those inappropriately written for clinical condition in which antibiotic use was not justified (prescription category F).
- Effect sizes (d-values) for differences between mean costs of prescribed antibiotics per prescription in prescription categories "A1 and A2", "A1 and B" or

A2 and B are 0.15 or below and hence statistically insignificant (Steyn, 2009:4-21; Utts & Hackard, 2007:582).

4.1.2.2.2 Results Evaluation and Discussion

Comparison of average costs of prescriptions by their categories did not show a trend that could be interpreted to determine the precise impact appropriate antibiotic prescribing may have on costs of antibiotic prescriptions in outpatient departments. Antibiotic prescriptions written appropriately are in principle expected to be more cost-effective and hence exhibit less average cost by category than those written inappropriately. The almost equivalent average cost of category A1 prescriptions to category B prescriptions or more precisely the slightly higher average cost of category A1 prescriptions as compared to average costs of category B prescriptions did not show this to be the case (Table 4.1.25).

In the category of prescriptions written for prevention of infections average costs of category D prescriptions were seen to be lower than average costs of category E prescriptions. This, however, did not enable conclusions of positive agreement of this result to what is expected in principle to be drawn because of the rather small number of prescriptions from which average costs of category E prescriptions were calculated. Based on calculated average costs of prescription categories given for treatment of infections as well as comparisons of mean costs of antibiotic prescription categories by effect size determinations (d-values < 8 and <5 in each compared pair of prescription categories) degrees to which antibiotics are written appropriately according to principles of rational antibiotic prescribing are not seen to have any significant impact on costs of antibiotic treatment in outpatient departments (Steyn, 2009:4-21; Utts & Hackard, 2007:582).

Of significant note, however, is the trend observed in the average costs of antibiotic prescriptions written appropriately for infections in which bacterial pathogens were either absolute (prescription category A1) or possible aetiologies (prescription category A2) on one hand and antibiotic prescriptions written inappropriately for treatment of infections (prescription category B) or for clinical conditions in which the use of antibiotics is not

justified on the other hand. Average costs of category A1 prescriptions are higher than average costs of category A2 prescriptions with the same being true for categories B and F prescriptions (Figure 4.1.9). While this trend does not indicate any impact on degrees to which indicated prescription categories are appropriately written, it does suggest one or both of the following in explanation:

- Prescribers' inclination towards prescribing more expensive antibiotics in infections with absolute bacterial aetiologies (category A1 prescriptions) compared to their inclinations to prescribing the less expensive drugs in situations of suspected infections (categories A2 and F prescriptions).
- Alternatively, the identification of prescription category A1 prescriptions being prescriptions mostly for treating skin and soft tissue and genitourinary tract infections on one hand and of category A2 prescriptions being antibiotic prescriptions for treating respiratory tract (Figure 4.1.8; Section 4.1.2.6, Table 4.1.28) as shown in results evaluation and discussion for Section 4.1.2.1 (**Prescription categorisation**) are indicative of antibiotics used in treating the former infections being more expensive than those used in treating the latter infections.

An explanation of prescribers' inclination to prescribing more expensive antibiotics in infections with absolute bacterial aetiologies being true would be suggestive of their positive correlation of the effectiveness of antibiotics in eradicating bacterial pathogens in clinical infections to their costs. Such, a correlation unfortunately would not necessarily be correct and may lead to wrong antibiotic choices.

4.1.2.3 Multiple antibiotic prescribing and the impact of antibiotic stock unavailability on prescribers' choice of antibiotics

Results of data analysis show the extent to which antibiotics are multiply prescribed. Prescribers' and their preferences and choices of antibiotics prescribers make preferentially in treating infections in outpatient departments are outlined in this section and discussed. "Choices of antibiotics" in the context of the study is defined as antibiotics prescribers would usually prescribe from lists of antibiotics known or made known to them as being available for their prescribing in the pharmacies of their practice hospitals. First, second or even third "choice" antibiotics would by this definition mean antibiotics prescribers prescribe:

- in first instances of their prescribing antibiotics in the assumption of their availability at the pharmacy;
- in second instances of their prescribing antibiotics when first choice prescribed antibiotics are not available and prescribers prescribe alternative choices from lists of alternative available antibiotics they are provided from the pharmacies of their hospitals; or
- in third instances of their prescribing antibiotics alternative to their second choices from available stock of antibiotics, following failure of pharmacies to still dispense such second choice antibiotics to patients.

4.1.2.3.1 Results

Of the total number of outpatient antibiotic prescriptions assessed, as Table 4.1.26 shows, prescriptions with single prescribed antibiotics accounted for 82.0%, while those with two, three , and four antibiotics prescribed antibiotics accounted for were 14.2%, 3.5% and 0.3% respectively.

- Prescriptions with single (1) prescribed antibiotics at Maluti hospital were 75.8% of all prescriptions assessed for the hospital while at Berea hospital no prescriptions with three (3) antibiotics were assessed.
- Prescriptions with four antibiotics were rare and seen only at Maluti and Scott hospitals and were only 2 out of 161 (1.2%) and 1 out of 77 (1.3%) assessed respectively for the two hospitals.
- No prescriptions with more than four (>4) antibiotics were seen and assessed for any study site.

Table 4.1.27 shows relative frequencies of prescriptions according to dispensed antibiotics being prescribers' first, second and third choices of antibiotics and whether or not prescribers' alternative choices of antibiotics were based on unavailability of their first choices. According to the table the following has become apparent:,

- Of the total of 865 antibiotic prescriptions assessed, prescriptions for antibiotics that were dispensed to patients as prescribers' first and second choices were respectively 97.6% and 2.4%.

- No antibiotics were prescribed and dispensed to patients as prescribers' third choice.
  - For all study site hospitals, dispensed prescriptions were between 96.0% and 98.8% of the case prescribers' first choice of antibiotics compare to prescriptions of prescribers' second choice antibiotics which were between 1.2% and 4.0% of the total number of dispensed prescriptions.
- Of the total number of alternative second choice antibiotics prescribed, 85.7% were prescribed for reasons of first choice not being available as against 14.3% for other reasons not specified.

Table 4.1.26: Frequencies of numbers of prescribed antibiotics per prescription according to study sites.

Study site	Prescriptions according to number of prescribed antibiotics										
	Single antibiotic prescribed		2 antibiotics prescribed		3 antibiotics prescribed		4 antibiotics		> 4 antibiotics prescribed		Total
	n	n%	n	n%	n	n%	n	n%	n	n%	n
Berea	21	84.0	4	16.0	0	0.0	0	0.0	0	0.0	**25**
Maluti	122	75.8	29	18.0	8	5.0	2	1.2	0	0.0	**161**
Motebang	135	81.3	28	16.9	3	1.8	0	0.0	0	0.0	**166**
Queen II	369	84.6	54	12.4	13	3.0	0	0.0	0	0.0	**436**
Scott	62	80.5	8	10.4	6	7.8	1	1.3	0	0.0	**77**
Total	709	82.0	123	14.2	30	**3.5**	**3**	**0.3**	**0**	**0.0**	**865**

Notation: n% calculations based on row totals

Table 4.1.27: Relative frequencies of prescriptions by study sites and according to ranks of prescriber's choices of dispensed antibiotics and basis of choices being unavailability of 1st choice prescribed antibiotics.

Study site	Number of prescriptions							Frequencies of alternative antibiotic choices being determined by factor of antibiotic availability				
	1st Choice		2nd Choice		3rd Choice		Total	Alternative choice determined by unavailability of 1st choice antibiotic		Alternative choice not determined by unavailability of 1st choice antibiotic		Total
	n	n%	n	n%	n	n%		n	n%	n	n%	
Berea	24	96	1	4.0	0	0.0	25	1	100	0	0.0	1
Maluti	155	96.3	6	3.7	0	0.0	161	5	83.3	1	16.7	6
Motebang	164	98.8	2	1.2	0	0.0	166	2	100	0	0.0	2
Queen II	425	97.5	11	2.5	0	0.0	436	10	90.9	1	9.1	11
Scott	76	98.7	1	1.3	0	0.0	77	0	0.0	1	100	1
Total	844	97.6	21	2.4	0	0.0	865	18	85.7	3	14.3	21

Notation: n% calculations based on row totals.

4.1.2.3.2 Results Evaluation and Discussion

- **The extent and effectiveness predictions of multiple antibiotic prescribing**

Infections can be caused by multiple bacterial pathogens with different antibiotic sensitivity patterns. As mentioned in discussions of results of investigations into the extent of multiple antibiotic therapy among inpatients (Section 4.1.1.3), multiple antibiotics are commonly employed in treating infections in medical practice and many prescribers would do so for reasons of covering all possible pathogens involved in given infections. Much as such uses of the class of drugs may be considered rational in certain clinical scenarios, the tendency on the part of prescribers to prescribe such therapy is often to act as cover-ups for diagnostic imprecision as Chambers (2001:1169) indicated. The potential misuse of the drugs in situations where components of the therapy may actually not be active against organisms implicated in the manifesting infection, make unacceptable the use of multiple antibiotics as the best option in infection management, particularly in the treatment of infections for which adequate reasons are not available to justify the use of each component of the multiple therapy. According to Duberke and Fraser (2005:1), multiple antibiotic therapies can offer some advantages in infection treatment by causing decrease in the emergence of resistance through an increase in the number of genetic elements necessary to express resistance. While this may be true in certain cases as seen in antibiotic use in tuberculosis treatment, he expressed doubts as to whether combination therapy decreases resistance rates of nosocomial bacteria since plasmids that confer resistance to multiple classes of antibiotics are common in the hospital environment. Studies of combination therapy he further noted actually have not shown improved patient outcomes with combination antibiotic therapy and some studies (Leibovici *et al.*, 1997) according to him even suggest that outcomes may be worse because of increased toxicity associated with such therapies. For these reasons the prescription of single antibiotics that are active against pathogens commonly implicated in infections for which they are prescribed as against the prescription of multiple antibiotics, is considered the most rational therapy option in treating infections.

With as much as 82.0% of all outpatient antibiotic prescriptions being prescriptions for singly prescribed antibiotics, mono antibiotic therapy is documented as prescribers' preferred approach to treating infections in outpatient departments of all study sites (Table 4.1.29). This accordingly suggests the observed comparatively very few cases in

which two or more antibiotics were prescribed as cases of infections in which prescription of multiple antibiotics were probably justified. Some treatment guidelines as exemplified by the Lesotho Standard Treatment Guidelines referenced below may recommend syndromic approach in the treatment of genitourinary tract infections if demonstrating clinical symptoms suggest much possible bacterial aetiology. In such cases multiple antibiotic therapies may be recommended for prescribing. Sexually transmitted diseases are classical cases in which multiple antibiotic therapy is the preferred treatment choice (Ministry of Health & Social Welfare, 2006: 64-67). In cases where such infections are diagnosed as uncomplicated urinary tract infections e.g. cystitis or pyelonephritis single antibiotics may more rationally be recommended for prescribing (Ministry of Health & Social Welfare, 2006: 58-59).

In the absence of data enabling the assessment of prescriptions to determine the effectiveness of prescribed antibiotics, treatment outcomes and hence the effectiveness of single antibiotic therapy as a dominant pattern of antibiotic prescribing in the treatment of infections among outpatients can only be predicted from activity patterns of antibiotics most commonly prescribed for the treatment of respective infection types encountered in outpatient departments (Section 4.1.2.5, Table 4.1.36) against common pathogens associated with them (Section 4.1.2.5, Table 4.1.34). Based on their frequencies of prescribing as shown in Table 4.1.36, antibiotics most likely to be prescribed as single antibiotic therapies in outpatient departments in the treatment of the respective four major infection types seen in outpatient departments are presumably

- ampicillin, co-trimoxazole, erythromycin and penicillin for *respiratory tract infections* (Ministry of Health & Social Welfare, 2006: 22-26);
- cloxacillin, ampicillin, penicillin, erythromycin for *skin and soft tissue infections* (Ministry of Health & Social Welfare, 2006: 147-153;
- penicillin, ampicillin, co-trimoxazole, erythromycin and metronidazole for dental and mouth and *gastrointestinal tract infections* (Ministry of Health & Social Welfare, 2006: 50&131-133); and
- ciprofloxacin, metronidazole, erythromycin, doxycycline/tetracycline for *genitourinary tract infections* (Ministry of Health & Social Welfare, 2006: 64-67).

As Figure 4.1.8 showed, no antibiotic prescription written in outpatient departments was based on results of culture sensitivity tests. This, by interpretation, implies that culturing and testing bacterial isolates from specimens taken from infected body sites for their sensitivities against formulary antibiotics are not routinely done in outpatient departments.

In terms of data availability for this research, this meant a lack of data on culture sensitivity test (CST) results with regard to bacterial pathogens commonly associated with infections originating from communal environments. Specimens analysed for their microbial compositions and testing of bacterial isolates for this research were obtained mainly from inpatients. This said however, if it is considered that patients are admitted to hospitals often for treatment following first time presentations of illnesses from their communities, it can be reasonably assumed that most infections for which patients are admitted are infections they contracted from their communities and that the majority of infections that are treated among inpatients, particularly in medical settings, are infections that originate from communal environments. With this assumption, it was thought reasonable to modify and extrapolate results of culture sensitivity tests carried out on specimens from inpatients as presented in Tables 4.2.4 and 4.2.5, Section 4.2.2, to cover outpatients. In the modification of the data records of bacterial pathogens more often associated with nosocomial than community infections were ignored. This was done to account for differences that exist between inpatient and outpatient CST data due to infections in the former patient group by organisms associated more with infections in hospitalised patients. By considering the antibiotic sensitivity patterns of pathogens in the modified data as provided by available data on culture sensitivity test results, a realistic estimation of the therapeutic effectiveness of antibiotics singly prescribed in outpatient departments for given infections can be made.

- **Theoretical basis of CST results data modification**

In the modification of CST results data to include pathogens commonly associated with infections seen and treated in outpatient departments as shown in Table 4.1.19, principles outlined below on pathogen associations with common infections which formed the basis of the exclusion of certain pathogens in the modified data were followed.

- Enterococci (E. *faecalis* and *E faecium*), except for their association with infections in debilitated elderly patients and diabetic foot infections which may also come from the communities, are associated with infections in hospitalised patients in whom the mucosal or epithelial barrier has been disrupted for example by catheterisation or instrumentation of any kind (Musher, 2005: 830). The pathogens were for this reason not considered as pathogens associated with infections commonly seen in outpatients.

- Streptococci, mainly *Streptococcus pneumoniae* and *Streptococcus pyogenes* are associated with various infections from the community (Elliot *et al.*, 2004:23 & 34; Musher, 2005: 808 824, 826 & 827) likewise gram-negative bacilli, comprising *Escherichia coli*, *Klebsiella* and *Proteus* spp (Russo, 2005: 881, 882, 883).

- Staphylococci, though associated mainly with skin infections from both communal and hospital environments (Lowy, 2005:817; Elliot *et al.*, 2004:28; Inglis, 2003: 57 & 58) and also with respiratory tract infections in specific clinical settings and patients, notably newborns and infants and intubated hospitalised patients, can be considered as a common pathogen associated with respiratory tract infections in community patients because of their associations with the infection type in the patient group, as sequelae to post-viral infections (Lowy, 2005:818).

- Except for *Staphylococcus saprophyticus* that is associated with urinary tract infections in young women, literature findings have not linked other staphylococci (*Staphylococcus aureus and Staphylococcus epidermidis*) with the development of genitourinary tract infections (Lowy, 2005:819; Stamm, 2002:1S; Elliot *et al.*, 2004: 28, 29). On the basis of the dominant isolation of *Staphylococcus aureus* from penile and vaginal swab specimens of inpatients and the high probability that such infections might be contracted from the community based on reasons given for the extrapolation of results of culture sensitivity tests to cover outpatients as well, the association of the pathogens with genitourinary tract infections among the Basotho (people of Lesotho) can be assumed and the effectiveness evaluation of prescribed antibiotics in treating the infection done in the view of staphylococci being one of prominent pathogens.

- *Haemophilus influenzae* (non-typable) is a known common cause of lower respiratory tract infections in adults, notably pneumonia and exacerbations of chronic obstructive airways disease and also of otitis media in children and sinusitis in adults while *H. influenzae* type b is mainly associated with childhood infections including meningitis, epiglottitis, cellulitis, otitis media and pneumonia (Murphy, 2005:865).

- *Neisseria gonorrhoea* isolated from vaginal swab specimens, even if isolated from inpatients must be considered as coming from the community because of the organisms' identification with sexual transmission and consideration as part of the spectrum of pathogens associated with genitourinary tract infections in outpatients (Ram & Rice, 2005:857).

- *Corynebacterium urealyticum* though predominantly a pathogen of the urinary tract and *Corynebacterium amycolatum* though the most common species among infection-related strains of *Corynebacterium* associated with urinary tract infections (and also with wound infections and infections related to the blood) (Lagrou *et al.*, 1998:10) were isolated at very low relative frequencies in penile swab specimens only and not in urine specimens (Section 4.2.2, Table 4.2.2). *Corynebacterium* though associated with urinary tract infections in outpatients may not, for reasons of their low rates of isolations from genitourinary urinary tract specimens, be considered as regular pathogens of the urinary tract to merit their initial targeting for antibiotic treatment in the patient group.

- Gram-negative bacilli as causative agents of skin and soft tissue infections in communal environments are seen mostly in specific clinical cases involving hosts with neuro-vascular compromise as seen for example in their implications in polymicrobial infections of decubitus ulcers in diabetic patients (Russo, 2005: 881,882). They may also be seen implicated in certain cases of cellulitis as noted for *E. coli* and *Klebsiella* (Madappa & Go, 2009:1; Russo 2005:881,882). The pathogens, however, are notably associated with many nosocomial infections and may be considered more of causative agents of surgical and other wound infections in hospitalised patients than being aetiologies of skin and soft tissue infections from communal environments generally.

- *Pseudomonas, and Acinetobacter* are recognised as common causes of hospital-acquired infections and may not be considered as pathogens commonly responsible for communal infections, (Inglis, 2003:249; Abdi-Ali *et al.*, 2005:196). This takes exception of ear infections in which the organisms are known to be the principal aetiological agent of otitis externa (Ohl & Pollack, 2005:891) and hence may be associated with ear infections emanating from the community.

- Anaerobic bacteria are found as commensals of mucosal surfaces including buccal mucosa, lower gastrointestinal tract and female genital tract mucosa and may only cause infections in these areas when mucosal barriers are compromised by surgery, trauma, tumour and ischemia or necrosis (Kasper, 2005: 940). The organisms for these reasons may not be considered as pathogens commonly involved in infections among outpatients.

On the basis of the above considerations lists of pathogens identified from study results as associated with infections in inpatients can be modified to provide lists of most probable pathogens likely to cause indicated major infections seen and treated in outpatient departments of study sites. These are as listed below.

Respiratory tract infections

α-haemolytic streptococci (*S. pneumoniae*), β-haemolytic streptococci (*S. pyogenes*), *Staphylococcus aureus*, *Staphylococcus epidermidis*, (gram-positive cocci); *Klebsiella, Haemophillus influenzae,* (gram-negative bacilli).

Genitourinary tract infections

Escherichia coli, *Klebsiella* spp, and *Proteus* spp, (gram-negative bacilli); *Staphylococcus aureus, Staphylococcus epidermidis,* α-haemolytic streptococci (*S. pneumoniae*), non-haemolytic streptococci (non-enterococci), and β-haemolytic streptococci (*S. pyogenes*) (gram-positive cocci); and *Neisseria gonorrhoea* (gram-negative cocci).

Skin and soft tissue infections (Ear infections excluded)

Staphylococcus aureus, Staphylococcus epidermidis, α-haemolytic streptococci (*S. pneumoniae*) β-haemolytic streptococci (*S. pyogenes*), (gram-positive cocci).

Skin and soft tissue infections (Ear infections included)

Staphylococcus aureus, Staphylococcus epidermidis, α-haemolytic streptococci (*S. pneumoniae*) β-haemolytic streptococci (*S. pyogenes*), (gram-positive cocci), *Pseudomonas* and *H. influenzae* (gram-negative bacteria associated with ear infections).

Gastrointestinal tract infections

Escherichia coli, *Klebsiella* and *Proteus* spp, *Salmonella, and Shigella* spp.

- **Estimations of effectiveness of singly prescribed antibiotics for infections among outpatients**

Local patterns of bacterial pathogen sensitivities to commonly prescribed antibiotics as shown in Tables 4.2.4 & 4.2.5.

On the assumption that the effectiveness of antibacterial agents in treating infections successfully correlates positively and directly with their activities against causative pathogens of the infection, one can predict chances of treating infections with known bacterial pathogens successfully using antibiotics with known activities against the bacterial pathogens causing the infection. Such predicted chances will be by this assumption, equivalent to the activities of the antibacterial agents against the pathogens known to be implicated in the given infection. By such considerations and using reported sensitivities of pathogens to given antibiotics (Tables 4.2.4 & 4.2.5) or calculated percentage overall activities (POAs) [Appendix 11] of given antibiotics against pathogens most likely to be implicated in single or mixed infections of anatomical sites to which they are associated, the effectiveness of single prescriptions of these antibiotics in treating infections for which they are most often prescribed can be evaluated. These were done and presented below for the common antibiotics seen to be prescribed for given infections treated in outpatient settings.

- **Ampicillin** prescribed singly will have about a 71.0% to 90.0% chance of treating *respiratory tract infections* successfully only in situations where streptococci are the only infecting pathogens in accordance with the antibiotic's corresponding activities against these pathogens (Table 4.2.4). In the event of staphylococci being implicated as causative agents of respiratory tract infections as the list of common

pathogens associated with the infection type as seen in outpatients suggests and if POA values of the antibiotic against all possible pathogens including *Klebsiella* spp likely to cause the infection are considered, a single prescription of the antibiotic in treating respiratory tract infections will have only about a 52% chance (Appendix 11(v) of treating the infections successfully.

- Single prescription of the antibiotic in treating *skin and soft tissue infections* similarly have chances of 46% [POA value: Appendix 11(ix)] only in treating the infections except in cases where streptococci are the sole implicating agents, in which case chances of 71.0% to 90.0% (Table 4.2.4) in treating the infections successfully would be expected. Ampicillin/amoxycillin is also documented by study results as the second most frequently prescribed antibiotic in treating *gastrointestinal infections* among outpatients as indicated above. Prescribed singly in treating the infection type the antibiotic will have only 16.0% to 28.0% (Table 4.2.5) chances corresponding to the activity of the antibiotic against gram-negative bacteria, of being used successfully for this purpose.
- Single prescribing of ampicillin may benefit patients only in situations of streptococci being sole causative agents as may be seen in respiratory tract infections and some types of skin and soft tissue infections like impetigo and erysipelas or cellulitis (Musher, 2005: 827). Single prescription of the antibiotic is predicted to have high treatment failures in situations of staphylococci being implicated as causative agents which, in the case of respiratory tract infections, may be recognised in patients coughing with bloody sputum as sequelae to viral infections (Lowy, 2005:818). Similarly poor treatment outcomes are predicted from single prescriptions of the antibiotic in treating skin and soft tissue infections which are largely associated with *Staphylococcus aureus* and *Staphylococcus epidermidis* as causative agents.

- **Co-trimoxazole** is prescribed in the treatment of *respiratory* and *gastrointestinal tract infections*, *genitourinary tract* and *skin and soft tissue infections* mainly (Table 4.1.36). Prescribed singly it has a 20.5% to 66.0% chance of treating respiratory tract infections successfully if streptococci were sole causative agents (Table 4.2.4) or 42% [POA values: Appendix 12(v)] if all pathogens associated with respiratory tract infections in outpatients including staphylococci and *Klebsiella* spp are considered. Similarly the antibiotic when prescribed singly, has chances of 10% to 35% only in treating successfully gastrointestinal infections (Table 4.2.5) and 34%

in treating uncomplicated urinary tract infections (POA value: Appendix 12(xiii) where gram-negative bacilli are considered the major implicating pathogens. Prescribed singly in treating skin and soft tissue infections, the antibiotic has chances of 20.5% to 66.0% chances of treating skin and soft tissue infections if streptococci were sole implicating pathogens or 38% chances of treating the infection (POA values: Appendix 12(ix) if staphylococci were to be considered as additional pathogens implicated in the infections. By these estimates single prescriptions of co-trimoxazole in the indicated infections are predicted to have poor treatment outcomes.

- **Erythromycin** and **penicillin** are prescribed for all four major infection types treated in outpatient departments, namely infections of the respiratory tract, gastrointestinal tract, genitourinary tract and skin and soft tissue (Table 4.1.36). Prescribed singly the two antibiotics would have chances of about 61.0% to 77.0% in successfully treating *respiratory tract infections* if streptococci were sole infecting pathogens (Table 4.2.4). They would similarly and respectively have chances of 47.0% to 67.0% or 23.5% to 31.4% in treating infections successfully if staphylococci and not *Klebsiella* were additionally implicated as causative agents of the infection (Table 4.2.4). The activities of the antibiotics against *Klebsiella* spp are not known and estimates of their effectiveness in treating respiratory tract infections implicated by the pathogens cannot be determined. Prescribed singly, the antibiotics may hence be used with moderate success in treating streptococcal respiratory tract infections. Single prescriptions of the antibiotics in treating *skin and soft tissue infections* are predicted to have chances of 31% for penicillin and 66% for erythromycin in treating the infections if all possible pathogens including staphylococci are causative agents of the infection (POA values: Appendix 12(ix). In the event of streptococci being the sole causative agents of the infection, the antibiotics would have the same treatment rate as predicted for respiratory tract infections if singly prescribed in treating the infection.

Local CST results data of gram-negative bacilli are not available for estimates of the effectiveness of singly prescribed dosage regimens of the antibiotics in treating gastrointestinal and urinary tract infections despite indications that the antibiotics are being used in treating these infections (Table 4.1.34). The antibiotics are however

classically known to be inactive against gram-negative bacilli (Petri, 2001:1251; Elliot *et al.*, 2004:53; Russo 2005:882) and their prescribing in these infections where the pathogens are causative agents are predicted to be highly ineffective. Erythromycin is prescribed in a syndromic approach together with other antibacterial agents in the treatment of genitourinary tract infections complicated with vaginal or urethral discharges presumably for its activity against *Clamydia trachomatis* which may be a causative agent of this infection (Ministry of Health & Social Welfare, 2006: 64-67). *Clamydia trachomatis* is intrinsically sensitive to macrolide antibiotics and the prescription of erythromycin in treating infections of the genitourinary tract in the way described is recommended (Petri, 2001:1251; Holmes, 2005:765).

- **Cloxacillin** was seen to be prescribed mainly in treating *skin and soft tissue* infections but also for *respiratory* and *genitourinary tract infection* (Table 4.1.34). The dominance of *Staphylococcus aureus* as the most prevalent causative agent in these infections (Figures 4.2.11, 4.2.13, 4.2.15 and 4.2.16) suggests the antibiotic, being a semi-synthetic penicillinase resistance penicillin, was prescribed mainly against *Staphylococcus aureus* as causative agents of these infections. Prescribed singly for skin infections the antibiotic has chances of 75% to 80% in successfully treating these infections if *Streptococcus pyogenes* and *Staphylococcus aureus* are implicating pathogens. In the event of *Staphylococcus epidermidis* and *Streptococcus pneumoniae* (other listed gram-positive cocci identified as commonly associated with skin and soft tissue infections among outpatients, Table 4.2.3) being the aetiological agents of these infections, single prescriptions of the antibiotic will have moderate chances of 50.0% to 66.0% in treating the infections successfully.

- **Ciprofloxacin** was seen to be prescribed mainly for *genitourinary tract infections* but also for *respiratory* and *skin and soft tissue infections* (Table 4.1.34). The antibiotic was seen to exhibit activities of 73.0% to 100% against all gram-positive cocci and gram-negative bacilli associated with major infections seen and treated among outpatients (Table 4.2.4). Prescribed as a single antibiotic in treating uncomplicated urinary tract infections caused mainly by gram-negative bacilli, the antibiotic has chances of 74% to 90% equivalent to its activity range against these known uropathogens (Table 4.2.5). Based on its calculated POA values which took into consideration incidences of isolation of streptococci from urine specimens,

single prescriptions of the antibiotic is estimated to have a 78% chance of treating uncomplicated urinary tract infections (POA values: Appendix 12(xiii). Single prescribing of ciprofloxacin in gastrointestinal infections on the basis of gram-negative bacilli being associated with such infections mostly (Russo, 2005: 881-883) is predicted to have chances of 74% to 90% equivalent to the antibiotics its activity range against these pathogens (Table 4.2.5).

Ciprofloxacin is documented in literature to have only moderate activity against gram-positive bacteria such as *Streptococcus pneumoniae* and *Enterococcus faecalis* and is for this reason not a drug of first choice in treating pneumococcal pneumonia particularly (British Medical Association & Royal Pharmaceutical Society, 2002:294). In the researcher's opinion, the antibiotic may also not be a drug of first choice in treating other infections like skin and soft tissue infections which are dominantly caused by gram-positive bacteria for the above reasons (Figure 4.2.11). These literature documentations notwithstanding and based on its calculated POA against common pathogens associated with respiratory tract and skin and soft tissue infections at study site hospitals, the antibiotic is estimated to have 78% [Appendix 21 (v)] and 77% (Appendix 12(ix) chances of treating lower respiratory tract infections among outpatients.

- **Doxycycline/Tetracycline** is prescribed mostly for genitourinary tract infections. The antibiotic is estimated to have only 19.0% to 32.0% chances of treating the infection type if its activity against gram-negative bacilli, the major pathogens associated with urinary tract infections among outpatients is considered (Table 4.2.5). Like erythromycin, the routine prescription of doxycycline/tetracycline in treating genitourinary tract infections is presumed to be for activities of the antibiotic against *Clamydia trachomatis* and not gram-negative bacilli. The antibiotic is intrinsically active against *Clamydia trachomatis* (Holmes, 2005:765) and is recommended as an alternative to erythromycin in the treatment of genitourinary tract infections complicated with urethral or cervical discharges (Ministry of Health & Social Welfare, 2006: 64-67). In accordance with its activities against gram-positive cocci as indicated in Table 4.2.4, single prescriptions of doxycycline/tetracycline is estimated to have about 72.0% chances of treating respiratory tract infections if causative pathogens were *Streptococcus pneumoniae*. In situations where

causative agents were staphylococci or *S. pyogenes* the antibiotic would be effective to the extent of 33.0% to 56.0% in treating infections of the respiratory tract according to its activity range against these pathogens (Table 4.2.4). Use of the antibiotics in treating skin and soft tissue infections will similarly be effective to the same extent as cases of respiratory tract infections in which staphylococci or *S. pyogenes* are causative agents. Percentage overall activities of the antibiotic against most probable pathogens likely to be implicated in respiratory tract and skin and soft tissue infections confers chances of 51% and 49% in treating the infections if the antibiotic is singly prescribed for the purpose [Appendixes 12(v) and 12(ix)]. By these considerations, doxycycline or tetracycline when singly prescribed may be effective in the empiric treatment of pneumococcal but not other streptococcal respiratory tract infections or skin and soft tissue infections.

- **The impact of unavailability of prescribed antibiotics on prescribers' choices of antibiotics**

Antibiotic selection in the empiric treatment of infections in principle must be based on sensitivity characteristics of infecting bacterial pathogens, either intrinsic or locally acquired. Based on this, an antibiotic selected in the treatment of a given infection can or cannot be substituted with a second antibiotic depending on degrees to which the activities of a prescribed first choice antibiotic against infecting pathogens are similar to those of available alternative antibiotic choices. Problems of antibiotic stock unavailability at study sites can be a factor that negatively affects the appropriate selection of antibiotics for the effective treatment of infections. Of the total 865 outpatient antibiotic prescriptions presented at the pharmacies of study site hospitals and which were assessed for this study, 97.6% were reported as prescribers' first choice antibiotics. Of the total number of assessed outpatient antibiotic prescriptions, 2.4% were reportedly dispensed as prescribers' second choice or second instance prescribed antibiotics. These were dispensed mostly for reasons of first choice antibiotics not being available.

The high 97.6% of antibiotic prescriptions dispensed being the first choice of prescribers indicated that the unavailability of prescribed antibiotics was not a factor that seriously limited prescribers' ability to select antibiotics which in their opinion would be most appropriate in the treatment of infections in outpatient departments.

The result support the view that the pattern of antibiotic prescribing established by this study as the true pattern of antibiotic prescribing characteristic to prescribers of the drug in Lesotho in situations where prescribers' ability to appropriately select antibiotics for prescription are not in any way compromised by unavailability of antibiotics of their choice in treating infections.

4.1.2.4 Determining the extent to which prescribers establish need for antibiotic use or presence of infections prior to prescribing antibiotics

The section outlines results of outpatient antibiotic prescription assessment to establish the extent to which prescribers establish the need for antibiotic use in treating clinical conditions patients present to them as a prerequisite to their prescribing the class of drugs. Criteria used in this assessment investigated how often prescribers, before their decision to prescribe antibiotics, establish

- presence of signs or symptoms of infections,;
- the absoluteness of infections being of bacterial aetiologies;
- anatomical sites of indicated infections;
- presence of potential sources of infections in cases where their assessment of the patient did not conclude a current diagnosis of an infection; and
- whether they establish presence of infections by objective assessment of patients or from symptoms only.

Results were evaluated and discussed from a perspective that focussed on establishing any realistic links between inappropriate prescribing of antibiotics and inappropriate diagnosis of presenting cases before antibiotic treatment is offered.

4.1.2.4.1 Results

Percentage frequency distribution of prescriptions by study site and according to prescribers' use of antibiotic need assessment criteria in determining patients' need for antibiotics as a first step before their decision to prescribe the class of drugs in outpatient departments is shown in Table 4.1.30. Of the total number of 865 prescriptions assessed the following have been established as percentage frequencies that prescribers carried out or did not carry out indicated activities in diagnostic workups

intended to establish the presence of infections before antibiotic prescriptions were made.

- In 85% of the cases prescribers established signs and symptoms of infections before their decisions to prescribe antibiotics in outpatients.
- Of the total number of prescriptions assessed for each study site, prescribers were seen to establish signs and symptoms of infections before prescribing antibiotics in 90.9% of the cases at Scott hospital, 88.0% at Motebang hospital, 84.5% at Maluti hospital, 84.0% at Berea hospital and 83.0% at Queen II hospital.
- In 38.0% of the times prescribers of all study sites identified signs and symptoms of diagnosed infections that were absolute for bacterial infections as against 62.0% (n= 536) when they did not.
- Of the total number of prescriptions assessed for each study site, prescribers were seen to identify signs and symptoms of infections that were absolute for bacterial infections in 88.8%, 49.7%, 45.5%, 36.1% and 34.6% of the cases at Berea, Maluti, Scott, Motebang and Queen II hospital respectively.
- Prescribers at all hospital sites of study prescribed antibiotics in 86.8% of the cases for cases in which anatomical sites of infections were identified. Of the total number of cases treated at individual study site hospitals, prescribers identified sites of infections in 90.9% of the cases at Scott hospital, 86.8% at Motebang, 88.2%,at Maluti, 85.8% at Queen II and 84% at Berea hospitals.
- Of the total number of antibiotic prescriptions assessed 0.4% were written for infections diagnosed with supporting objective data. The rest (99.6%) were written upon prescribers' subjective assessment of patients based on presenting clinical symptoms.
- Of the total number of antibiotic prescriptions assessed for all study site hospitals 4.0% (n=35) were prescribed for prophylaxis of infections in patients with either potential sources of infections or disease conditions that promote infections by bacterial pathogens.
- Of the total number of prescriptions assessed for individual study sites, 6.2% were prescribed for prophylaxis at Maluti hospital, 4.8% at Queen II hospital, 2.6% at Scott hospital and 1.2% at Motebang hospital. No antibiotics were seen to be prescribed for prophylaxis at Berea hospital.

Table 4.1.28 Percentage frequency distribution of prescriptions by study sites and according to prescribers' use of antibiotic need assessment criteria in determining patients need for antibiotics

Antibiotic need assessment criterion	Frequencies of prescribers' basement of patients need for antibiotic treatment on antibiotic need assessment criterion														
	Berea					Maluti					Motebang				
	Assessment based on criterion		Assessment not based on criterion		Total	Assessment based on criterion		Assessment not based on criterion		Total	Assessment based on criterion		Assessment not based on criterion		Total
	n	n%	n	n%	n	n	n%	n	n%	n	n	n%	n	n%	n
Signs and symptoms of infection present	21	84.0	4	16.0	25	136	84.5	25	15.5	161	146	88.0	20	12.0	166
Signs and symptoms absolute for bacterial infection	22	88.0	3	12.0	25	80	49.7	81	50.3	161	60	36.1	106	63.9	166
Site of infection identified	21	84.0	4	16.0	25	142	88.2	19	11.8	161	144	86.8	22	13.2	166
Potential source of infection present	0	0.0	25	100	25	10	6.2	151	93.8	161	2	1.2	164	98.8	166
Presence of infection established by objective data	0	0.0	25	100	25	0	0.0	161	100	161	1	0,6	165	99.4	166
Presence of infection inferred from symptoms alone	25	100	0	0.0	25	161	100	0	0.0	161	165	99.4	1	0.6	166
	Queen II					Scott					Total				
	Assessment based on criterion		Assessment not based on criterion		Total	Assessment based on criterion		Assessment not based on criterion		Total	Assessment based on criterion		Assessment not based on criterion		
	n	n%	n	n%	n	n	n%	n	n%	n	n	n%	n	n%	
Signs and symptoms of infection present	362	83	74	17.0	436	70	90.9	7	9.1	77	735	85.0	130	15.0	865
Signs and symptoms absolute for bacterial infection	151	34.6	285	65.4	436	35	45.5	42	54.5	77	329	38.0	536	62.0	865
Site of infection identified	374	85.8	62	14.2	436	70	90.9	7	9.1	77	751	86.8	114	13.2	865
Potential source of infection present	21	4.8	415	95.2	436	2	2.6	75	97.4	77	35	4.0	830	96.0	865
Presence of infection established by objective data	1	0.2	435	99.8	436	1	1.30	76	88.7	77	3	0.4	862	99.6	865
Presence of infection inferred from symptoms alone	434	99.5	2	0.5	436	77	100	0	0.0	77	862	99.6	3	0.4	865

Notations: n% value determinations based on row totals

4.1.2.4.2 Results evaluations and Discussion

Establishing the presence and type of aetiological agents implicated in a given diagnosed case of infection is a requirement for determining the need and choice of treatment appropriate for treating that infection.

While clinical presentations of infections provide essential clues as to what agents could possibly be their causes, the existence of similarities in symptoms of infections caused by different pathogenic microbial agents at certain anatomical sites make it rather difficult in certain cases to attribute the cause of infections to a particular type of microbial agent based on symptoms of the infection alone. As an example of similarities in symptoms of infections caused by different pathogenic microbial agents at certain anatomical sites, reference is made to a position paper by Gonzales *et al.* (2001:493) where it was indicated that symptoms of presence of purulent nasal discharge and purulent sputum on which physicians often rely to assign bacterial causes to acute respiratory illnesses such as acute rhinosinusitis and acute bronchitis, are also common in patients with upper respiratory tract infections with viral aetiologies.

Similarly cough with purulent bloody sputum may be symptoms of pulmonary tuberculosis (Raviglione & Obrien, 2005:957) and also of *Staphylococcus aureus* infections of the respiratory tract as sequelae of infections of the tract by viral agents (Lowy, 2005:818).

Vaginal discharges observed in certain cases of genitourinary tract infections may also be due to infections of *Clamydia trachomatis* and *Neisseria gonorrhoea* (Holmes, 2005:765). This difficulty of attributing the cause of infections in certain cases to a particular type of microbial agent based on symptoms of the infection alone dictates that proper diagnostic workups that would differentiate infections caused by one type of microbial agent from another to be done in order to determine causative agents responsible for given infections to enable their appropriate treatment.

Criteria used in the assessment of prescriptions for this study tested the extent to which prescribers carry out diagnostic workups to be able to establish presence of bacterial pathogens as causes of infections before they make decisions to prescribe antibiotics. Absoluteness of infections being of bacterial aetiologies can be determined through a comparative assessment of findings on physical examination of patients and the nature of presenting symptoms which, in some cases, more strongly suggests one aetiological

agent as cause of a given infection than the other. According to Gonzales *et al.* (2001: 493) for example, when additional predictors of bacterial rhinosinusitis such as illness lasting for more than seven days are absent, purulent nasal discharge and purulent sputum are weak predictors of bacteria infection in adults with upper respiratory infections. As the author further indicated purulence occurs when inflammatory cells or sloughed mucosal epithelial cells are present and can result form either viral or bacterial infection. The degree to which such deferential assessment to establish aetiological agents causing an infection can be successfully done will greatly draw on the prescribers' experience and methodological approach in the interpretations of clinical findings *vis a vis* the nature of presenting symptoms of the infection. This is particularly true with infections of anatomical sites like the upper respiratory tract where similarities in symptoms of viral and bacterial infections are very pronounced. In the absence of strong clinical evidences suggesting the presence of one microbial pathogen as an aetiological agent over another in a given infection, use of objective data obtained from results of laboratory tests and x-rays of infected anatomical sites may become the only dependable means to differentially determine causative microbial agents of an infection.

- **Assessing the extent to which prescribers establish need of antibiotics prior to their prescribing of the drugs.**

Results of analysis to determine prescription conformity to criteria used to determine patients' need for antibiotics before decisions to prescribe such drugs in outpatient departments showed that of the total of 865 cases studied, the majority 85% were cases for which prescribers identified signs and symptoms indicating the presence of infections. Only in 38% of cases however, were such signs and symptoms considered to be absolute for bacterial infections (Table 4.1.28). Results further showed that 15% and 62% of the prescriptions were written respectively in absence of signs and symptoms suggesting infections or were written based on signs and symptoms that do not establish the absolute presence of bacterial pathogens as aetiological agents of diagnosed infections (Table 4.1.28). An interpretation of this established a majority of cases (47%) for which antibiotics were prescribed for cases in which identified symptoms of infections were not necessarily symptoms of bacterial infections. Use of objective data to confirm infections in the patient group were seen in only 0.4% of cases.

The majority of prescribers at all study sites (86.5%) prescribed antibiotics in outpatient departments of study sites for infections for which sites of infections were identified (Table 4.1.28). This indicates high chances of antibiotics being appropriately prescribed for the empiric treatment of infections in accordance with antibiotic prescribing principles which require that sites of infections be identified in diagnostic workups to establish the presence of infections. This said though, it is important to note that identification of a site of infection in a diagnostic workup should be followed by precise diagnosis of the infection for a prescriber to be able to determine presumptuously implicating bacterial pathogens for appropriate targeting as antibiotics are prescribed.

Prescribers as deduced from the above result evaluations, were observed generally for over 80% of the times and equally at all outpatient departments of study sites, to adhere to principles of establishing both the presence of signs and symptoms indicative of bacterial infections and also the sites of such infections before prescribing antibiotics in the treatment of infections. Close similarities exist between signs and symptoms of bacterial infections and infections of some other microbial pathogens as stated in earlier paragraphs. On the basis of this and with the exception of signs and symptoms recognised as being absolute for bacterial infections, identifying signs and symptoms as well as site of infection as principles to be followed in antibiotic prescribing, may result in establishing presence of microbial infections that may not necessarily be of bacterial aetiologies. Antibiotics prescribed appropriately in accordance with these principles may actually be prescriptions for infections that may or may not have bacterial pathogens as absolute causative agents. Bacterial and viral infections of the respiratory tract, particularly infections of the upper respiratory tract, notably manifest with signs and symptoms that are nearly indistinguishable (Gonzales *et al.*(2001:493). Signs and symptoms indicative of infections of the tract as well as the anatomical site of these infections are easily established. This makes it most likely for antibiotic prescriptions given for their treatment to be considered appropriate especially if appropriateness assessment criteria used are based on prescribers' adherence to the principle of having to establish the presence of bacterial infection by establishing signs and symptoms and also the anatomical site of the infection. Upper respiratory tract infections are treated mainly in outpatient settings and antibiotic prescriptions given for their treatment for these reasons as explained are likely to be adjudged appropriate. This to a great extent explains why the majority of outpatient antibiotic prescriptions (78.4%) were found to be

appropriately written according to results reported for prescription assessment in Section 4.1.2.1. The methodology as used in prescription assessment for the study however capably distinguished prescriptions written appropriately for infections with absolute bacterial aetiologies (prescription category A1) from those considered appropriate but observed to be given for infections that may have bacterial pathogens as probable causative agents (prescription category A2).

The proportions of antibiotic prescriptions written in cases for which symptoms of infections were absolute for bacterial infections (38%) and cases in which identified symptoms of infections were not necessarily symptoms of bacterial infections (47%) relate very closely to relative frequencies of antibiotic prescriptions classified as prescription categories A1 and A2. Interpreted in the light of prescribers' demonstrated abilities to identify sites of infections in diagnostic workups establishing presence of bacterial infections, the pattern is seen as highlighting a problem of prescribers' gross inability to differentiate bacterial from non-bacterial infections as diagnosed for identified sites of infections. Since antibiotics needed to be prescribed for bacterial infections to be of therapeutic benefit to patients the show of prescribers' inability to differentiate bacterial and non-bacterial aetiologies of certain types of infections is seen as problem that needs redress to increase the chances of better antibiotic treatment outcomes of infections.

4.1.2.5 Determining leading infections and antibiotics most commonly prescribed for their treatment

Results of analysis of patient records to establish leading infections and antibiotics most commonly prescribed for their treatment are outlined, evaluated and discussed in this section. Diagnoses, symptoms or symptom complexes for which prescribers prescribe antibiotics in both inpatient and outpatient departments are as listed in Tables 4.1.15 and 4.1.16.

Infections of respective anatomical sites as prescribers indicated have been grouped together and analysed for their frequencies of use, epidemiological trends of occurrence within respective study sites and associations with prescribed antibiotics. Results were evaluated and discussed.

Determining frequencies of prescribed antibiotics: Points of consideration

Points taken into consideration in determining frequencies of presentations of infections and of prescribed antibiotics as shown in 4.1.30 and 4.1.31 were as stated for similar determinations for inpatient prescription records (Section 4.1.1.4). The procedure of counting each antibiotic in multiple antibiotic prescriptions as being prescribed for each infection in cases of concurrently diagnosed infections was identified as a limitation of the study. The possible impact of this limitation on the results of the study are discussed in Section 4.1.2.5.2.

4.1.2.5.1 Results

Prescriber indicated diagnoses suggestive of infections of various anatomical sites for which antibiotics were prescribed or symptoms prescribers specified as indicating such infections and frequencies of such diagnoses or use of such symptoms to indicate infections of given anatomical sites in outpatient departments are shown in Tables 4.1.29, 4.1.30, 4.1.31 and 4.1.32.

- **Frequencies of prescribers' use of diagnostic terms to describe infections of diagnosed anatomical sites**

- **Respiratory tract infections**

Of the total number of cases treated as infections in outpatient departments, 440 were diagnosed as respiratory tract infections. Table 4.1.29 shows that, of this total,

- 40.2% were diagnosed as infections of the upper respiratory tract according to definitions provided by Gonzales *et al.* (2001:491) for "upper respiratory tract infections" (URTI) but excluding otitis media. By these definitions URTI is considered as acute infection of the respiratory tract with no prominent localising clinical features with signs and symptoms denoting sinusitis, pharyngitis, bronchitis, otitis media and nasopharyngitis (the common cold). Various diagnostic terms prescribers indicated in patients' case notes as URTI with percentage frequencies of their indications of such terms include "upper respiratory tract infections" (20.2%) "pharyngitis, laryngitis and tonsillitis" (13.0%), "bronchitis" (6.4%) "sinusitis" (0.7%);
- 7.5% were diagnosed as "otitis media"/"otitis externa";

- 6.6% were diagnosed as infections of the lower respiratory tract and indicated as "lower respiratory tract infections (LRTI)" (1.1 %), "pneumonia" or pneumonia with tuberculosis" or "silicosis pneumonia" (5.5%) ;
- 9.8% were diagnosed and indicated as "respiratory tract infections" ; and
- 35.2% were treated as respiratory tract infections based on presence of respiratory symptoms indicated singly or as complexes of symptoms and included cough, cough with coloured sputum, cough with blood stain, cough with fever, chest pain, sore throat, fever etc.

- **Genitourinary tract infections**

Genital and urinary tract infections diagnosed as such and treated in outpatient departments of study sites were altogether 141.

- Of this number and as indicated in Table 4.1.30(a), 30.5% were cases of uncomplicated urinary tract infections (UTI) and urinary tract infections diagnosed concurrent with other genital infections. Other genital infections diagnosed without symptoms of UTI constituted 65.9% of the total diagnosed cases of genital and urinary tract infections.
- Of the total number of diagnosed cases of uncomplicated UTI and UTI diagnosed concurrently with other genital infections as indicated in Table 4.1.30(b), 65.1% were diagnosed as uncomplicated UTI and 34.9% as UTI complicated with vaginal and penile discharges.
- Diagnosis of uncomplicated UTI were variously indicated in patient case notes as "urinary tract infections" without indications of symptoms (11.6%), or indicated by symptoms of the infection. These included with their frequencies of indications "burning on micturition" (30.2%), "hot urine" (11.6%), dysuria" (7.0%), and "bloody or coloured urine" (5.2%).
- Observed diagnosed cases of UTI complicated with other genital infections included cases of UTI diagnosed concurrently with urethritis or cervicitis. These were indicated by prescribers as "burning on micturition with vaginal or penile discharges" (16.3%) and "dysuria with vaginal or penile discharges) (18.6%).

Table 4.1.29 Frequencies of use of diagnostic terms, symptoms and symptom complexes in categorising respiratory tract infections in outpatient departments

Diagnostic terms, symptoms or symptom complexes	Frequency	Percentage frequency
	n	n%
Upper respiratory infection	89	20.2
Pharyngitis or Tonsilitis or laryngitis	57	13.0
Bronchitis	28	6.4
Sinusitis	3	0.7
Subtotal (Diagnosis of upper respiratory tract infection)	**177**	**40.2**
Otitis media/externa	33	7.5
Subtotal (Diagnosis of otitis media/externa)	**33**	**7.5**
Respiratory tract infections	43	9.8
Subtotal (Respiratory tract infection indicated without specific diagnosis)	**43**	**9.8**
Diagnosed TB treated as respiratory tract infection	3	0.7
Subtotal (Tuberculosis treated as respiratory tract infection)	**3**	**0.7**
Lower respiratory infection	5	1.1
Pneumonia /pneumonia with TB/ silicosis pneumonia/PCP)	24	5.5
Subtotal (Diagnosis of Lower respiratory tract infection	**29**	**6.6**
Symptoms or symptom complexes only used to indicate disease condition of respiratory tract (Coughs with or without any description, chest pain, shortness of breath with or without fever, nasal congestion)	155	35.2
Subtotal (Use of symptoms to indicate presence of respiratory tract infection)	**155**	**35.2**
Total	**440**	**100**

- Diagnosis of uncomplicated UTI were variously indicated in patient case notes as "urinary tract infections" without indications of symptoms (11.6%), or indicated by symptoms of the infection. These included with their frequencies of indications "burning on micturition" (30.2%), "hot urine" (11.6%), dysuria" (7.0%), and "bloody or coloured urine" (5.2%).
- Observed diagnosed cases of UTI complicated with other genital infections included cases of UTI diagnosed concurrently with urethritis or cervicitis. These were indicated by prescribers as "burning on micturition with vaginal or penile discharges" (16.3%) and "dysuria with vaginal or penile discharges) (18.6%).

- **Gastrointestinal tract (and mouth) infections**

Of the total number of cases treated as infections in outpatient departments, 75 were diagnosed as gastrointestinal infections. Of this number as shown in Table 4.1.31,

- 49.3% were altogether indicated as dental and mouth infections or tooth extraction. Dental and mouth infections represented 33.3% and cases of tooth extraction 13.3% of total prescriber diagnosed gastrointestinal infections. Two cases of parotiditis representing 2.6% of total diagnosed gastrointestinal infections were diagnosed and indicated as such;
- 32.0% were diagnosed as infections of the gastrium or abdomen and the intestinal tract and were indicated variously as "abdominal pain" (13.3%), "gastritis" (1.3%), "gastroenteritis" (28.0%) and "gastrointestinal infection" (4.0%); and
- 4.0% were diagnosed and indicated as "anal sores/perianal sores";

Table 4.1.30 (a) Frequencies of use of diagnostic terms and symptoms in categorising genitourinary tract urinary tract infections in outpatient departments

Indicated diagnosis/ symptoms	Frequencies of indications	
	n	n%
Diagnosis of UTI (no indication of symptoms)	5	3.5
Burning on micturition	13	9.2
Bloody or coloured urine	2	1.4
Dysuria	3	2.1
Hot urine	5	3.5
Subtotal (Uncomplicated UTI)	**28**	**19.6**
Burning on micturition with vaginal discharge	7	5.0
Dysuria with vaginal discharge	8	5.7
Subtotal (UTI concurrent or vaginal or penile discharges	**15**	**10.6**
Total Uncomplicated UTI + UTI concurrent with STD	**43**	**30.5**
Penile discharge	10	7.1
Vaginal discharge (no description	34	24.1
Vaginal discharge (yellowish and purulent)	16	11.3
Vaginal discharge (white)	9	0.64
Vaginal discharge (clear)	2	1.4
Pelvic inflammatory disease	3	2.1
Diagnosis of STI	6	4.3
Vaginitis	3	2.1
Orchitis	3	2.1
Septic abortion	1	0.7
Genital ulcers/herpetic ulcers	4	2.8
Genital itches	6	4.3
Vaginal candidiasis	1	0.7
Subtotal genital infections without symptoms of UTI	**98**	**69.5**
Total	**141**	**100**

Table 4.1.30 (b) Frequencies of use of diagnostic terms and symptoms in categorising urinary tract urinary tract infections in outpatient departments

Indicated diagnosis/ symptoms	Frequencies of indications	
	n	n%
Diagnosis of UTI (no indication of symptoms)	5	11.6
Burning on micturition	13	30.2
Bloody or coloured urine	2	5.7
Dysuria	3	7.0
Hot urine	5	11.6
Subtotal (Uncomplicated UTI)	**28**	**65.1**
Burning urine with vaginal discharge	7	16.3
Dysuria with vaginal discharge	8	18.6
Subtotal (UTI concurrent or vaginal or penile discharges	**15**	**34.9**
Total Uncomplicated UTI + UTI concurrent with STD	**43**	**100**

- **Skin and soft tissue infections**

A total of 155 cases were diagnosed and treated with antibiotics in outpatient departments as skin and soft tissue infections. Of this total number as indicated in Table 4.1.32,

- 61.9% were diagnosed as bacterial infections of the skin and soft tissues and indicated as "abscesses, swellings pustules or furuncles" (24.5%), "acne" (2.6%), "impetigo" (3.9%), "cellulitis" (2.6%) and "septic ulcers or lesions" (27.7%);
- 21.9% were dermatological conditions non-indicative of infections of skin and soft tissues with bacterial pathogens commonly associated with infections at the site. These, as prescribers' indicated, included "skin rashes" (16.1%), "scabies" (3.9%) "insect bites" (0.6%) "seborrhoea" (0.6%), and "leprosy" (0.6%);
- 5.2% were diagnosed as "eye infections" and indicated as such; and
- 11.6% were diagnosed non-septic cuts or wounds providing portals to bacteria infections. These included as prescribers' indicated, "lacerations and bruises" (4.5%), "deep wounds including stab or gunshot wounds" (2.6%), "surgical wounds" (2.0%), "burns" (2.0%) and animal bites (0.1%).

Table 4.1.31 Frequencies of use of diagnostic terms, symptoms and symptom complexes in categorising gastrointestinal infections in outpatient departments.

Diagnostic term	Frequency	Percentage frequency
	n	n%
Dental and mouth infection	25	33.3
Tooth extraction	10	13.3
Parotiditis	2	2.6
Subtotal (Dental and mouth infections)	**37**	**49.3**
Abdominal pain	10	13.3
Gastritis	1	1.3
Gastroenteritis	21	28.0
Gastrointestinal infection	3	4.0
Subtotal (gastric/abdominal infections)	**24**	**32.0**
Anal sores/perianal ulcers	3	4.0
Subtotal (Anal sores)	**3**	**4.0**
Total	**75**	**100**

Table: 4.1.32 Frequencies of use of diagnostic terms, symptoms and symptom complexes in categorising skin and soft tissue infections in outpatient departments

Diagnostic term	Frequency	Percentage frequency
	n	n%
Abscesses(swellings, pustules, furuncles)	38	24.5
Acne	4	2.6
Cellulitis	4	2.6
Impetigo	6	3.9
Septic ulcers/lesions	43	27.7
Subtotal (Bacteria infections of skin & Soft tissue)	**96**	**61.9**
Insect bites	1	0.6
Leprosy	1	0.6
Skin rashes	25	16.1
Seborrhoea	1	0.6
Scabies	6	3.9
Subtotal (dermatological conditions non indicative of absolute bacterial infections)	**34**	**21.9**
Animal bites	1	0.6
Burns	3	2.0
Lacerations & bruises (non septic)	7	4.5
Surgical wounds (non septic)	3	2.0
Deep wounds (Stab or gunshot wounds (non septic)	4	2.6
Subtotal (non infective cuts or wounds	**18**	**11.6**
Eye infections	8	5.2
Subtotal (Bacteria infections of eye	**8**	**5.2**
Total	**155**	**100**

- **Epidemiology of diagnosed infections**

Table 4.1.33 shows the percentage frequencies of variously diagnosed infections among outpatients at respective study sites. Figure 4.1.4.11 on the other hand shows percentage frequency distribution of all diagnosed cases including non-infectious diseases for which antibiotics were prescribed among outpatients at study sites.

Of all 931 cases for which antibiotic prescriptions were given as shown in Figure 4.1.11,

- 88.3% and 11.7% were diagnosed as conditions respectively indicative of infectious and non-infectious diseases;
- Of all cases diagnosed as infections, 53.5%, 18.9%, 17.2%, 9.1%, 0.1% and 1.2% were respectively cases of respiratory tract infections, skin and soft tissue infections, genitourinary tract infections, gastrointestinal tract infections, bone infections and pyrexias of non-indicated origins;

Table 4.1.33 Frequencies of diagnosis and treatment of infection types among outpatients at study sites

Clinical Conditions	Frequencies infection types by study sites											
	Berea		Maluti		Motebang		Queen II		Scott		Total	
	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
Respiratory tract infections	16	69.6 (3.6)	62	39.5 (14.1)	111	68.9 (25.2)	203	51.5 (46.1)	48	60.0 (10.9)	440	53.5 (100)
Gastrointestinal tract infections	4	17.4 (5.3)	17	10.8 (22.7)	9	3.3 (12.0)	41	10.4 (54.7)	4	5.0 (5.3)	75	9.1 (100)
Genitourinary tract infections	0	0.0 (0.0)	42	26.8 (29.8)	26	15.9 (18.4)	58	14.7 (41.1)	15	18.8 (10.6)	141	17.2 (100)
Skin and soft tissue infections	3	13.0 (1.9)	34	21.7 (21.9)	20	10.6 (12.9)	85	21.6 (54.8)	13	16.3 (8.4)	155	18.9 (100)
Bone infections	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	1	0.3 (100)	0	0.0 (0.0)	1	0.1 (100)
Pyrexia with unknown origin	0	0.0 (0.0)	2	1.3 (20.0)	2	1.3 (20.0)	6	1.5 (60.0)	0	0.0 (0.0)	10	1.2 (100)
Sub totals (Cases of infections)	**23**	**100**	**157**	**100**	**168**	**100**	**394**	**100**	**80**	**100**	**822**	**100; 87.4**
Diagnoses non-indicative of bacterial infections	5	2.0 (4.5)	23	12.8 (21.1)	15	9.0 (13.8)	62	13.6 (56.9)	4	4.8 (3.6)	109	11.7 (100)
Total	**28**	**100**	**180**	**100**	**183**	**100**	**456**	**100**	**84**	**100**	**931**	**100**

Notation: n% calculation in bracket is based on row totals,
n% calculation not in bracket based on column totals

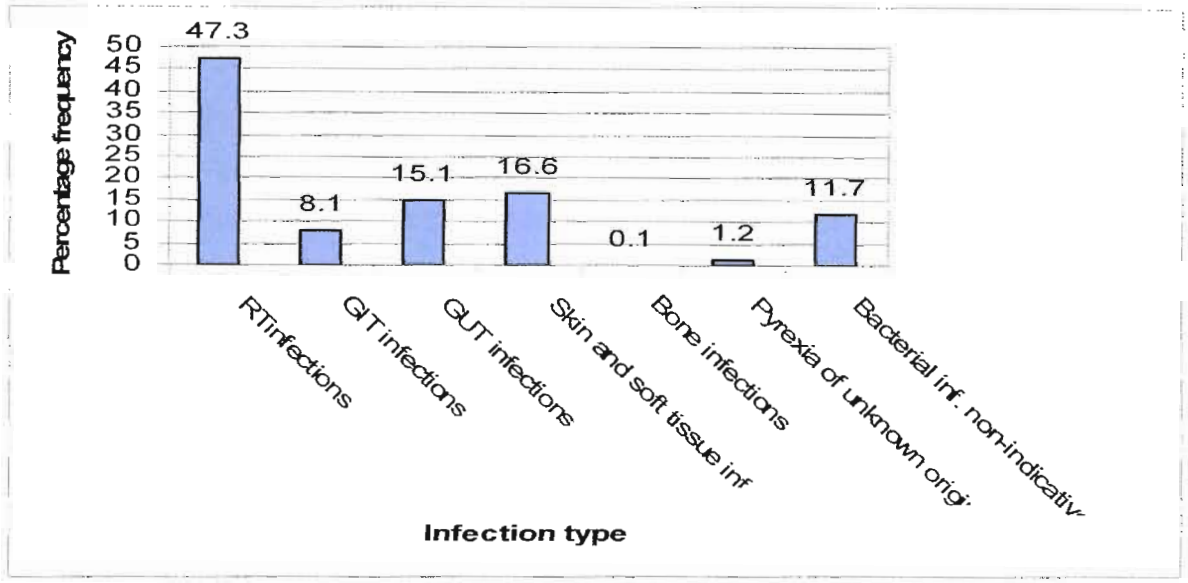

Figure 4.1.11 Percentage frequencies of prescriber diagnosed cases of indicated infection types among outpatients at study sites

- **Percentage frequencies of presentations of infection types at study site hospitals**

Respiratory tract infections

- Respiratory tract infections constituted 53.5% (n = 440) of all diagnosed cases of infections at outpatient departments of study site hospitals and represented 43.7% of all cases treated with antibiotics. Of this number, 46.1% were seen at the Queen II hospital, 25.2% at the Motebang hospital and 14.1%, 10.9% and 3.6% respectively at Maluti, Scott and Berea hospitals.
- Relative to other infections seen and treated at individual study site hospitals the infections presented at highest rates of between 51.5% and 69.6% at all study site hospitals.

Skin and soft tissue infections

- A total 18.9% (n = 155) of diagnosed cases of infections, representing 16.6% of all cases treated with antibiotics, were diagnosed and treated as skin and soft tissue

infections at all study sites. Of this number 54.8%, 21.9%, 13.0% 12.9%, 8.4% and 1.9% were respectively diagnosed and treated at Queen II, Maluti, Berea, Motebang and Scott hospitals.

- Percentage frequencies at which the infection types presented relative to other infections at individual study site hospitals were 21.7% for Maluti hospital, 21.6% for Queen II hospital, 16.3% for Scott hospital and 10.6% and 5.0% for the Motebang and Berea hospitals respectively.

Genitourinary tract infections

- Of all cases of infections diagnosed and treated at study sites genitourinary tract infections constituted 17.2% (n = 141) and represented 15.1% of all cases treated with antibiotics at the sites during the period of study. Of this number 41.1% were seen and treated at Queen II hospital, 29.8% at Maluti hospital, 18.4% at Motebang hospital and 10.6% at Scott hospital.
- Rates at which the infection presented at individual study site hospitals relative to other infections were 26.8% for Maluti hospital, 18.8% for Scott hospital, 15.9% for Motebang hospital and 14.7% for Queen II hospital.
- No cases of genitourinary tract infections were seen and treated at the Berea hospital during the period of study.

Gastrointestinal tract infections

- Infections of the gastrointestinal tract that presented at study sites during the period were 75 and constituted 9.1% of all diagnosed cases of infections or 8.1% of all cases for which antibiotics were prescribed. Of this number, a majority 54.7% were seen and treated at the Queen II hospital. Lower percentage proportions of 22.7%, 12.0% and 5.3% each were seen and treated at the Maluti and Motebang hospitals and the Berea and Scott hospitals.
- Prevalence rates of the infection relative to other infections at respective study sites were 17.4% for Berea hospital, 10.8% for Maluti hospital, 10.4% for Queen II hospital, and 5.0% and 3.3% for Scott and Motebang hospitals.

Pyrexia of unknown origin

- Pyrexia for which no causes were indicated but which were treated as infections represented 1.3% of all cases diagnosed and treated as infections at study sites. Of this number of such cases 60.0% (6 out of 10) were seen and treated at the Queen II hospital and 20.0% (2 out of 10) each at the Maluti and Motebang hospitals.

Bone infections

- Only one (1) case of bone infection was reportedly seen and treated at the Queen II hospital outpatient department during the period of study.

Antibiotic treated clinical conditions non-indicative of bacteria infections.

- Of a total of 11.7% (n = 109) of cases of clinical conditions non-indicative of bacterial infections that were treated with antibiotics, the majority 56.9% were from Queen II hospital. This is in comparison with much lower percentage proportions of 21.1% , 13.8%, 4.5% and 3.6% of such cases that were treated as infections at the Maluti, Motebang, Berea and Scott hospitals.

- **Antibiotics most commonly prescribed in outpatient departments**

- **Relative frequencies of prescribed antibiotics**

Of all routinely prescribed antibiotics as shown in Figure 4.1.12, **ampicillin (amoxycillin)** with a 24.8% relative frequency of prescribing was seen as the most frequently prescribed antibiotic at study site outpatient departments. Indicated with their rates of prescribing, it is followed in that order by **co-trimoxazole** (18.8%), **erythromycin** (16.7%), **cloxacillin** (9.7%) and **penicillin** (8.5%), **metronidazole** (7.2%), **ciprofloxacin** (4.5%), **doxycycline** (4.4%) and **tetracycline** (2.2%). Others included **nitrofurantoin** (1.0), **ceftriaxone** (1.1) and **gentamicin, nalidixic acid and chloramphenicol** which were each prescribed at relative frequencies of 0.2%.

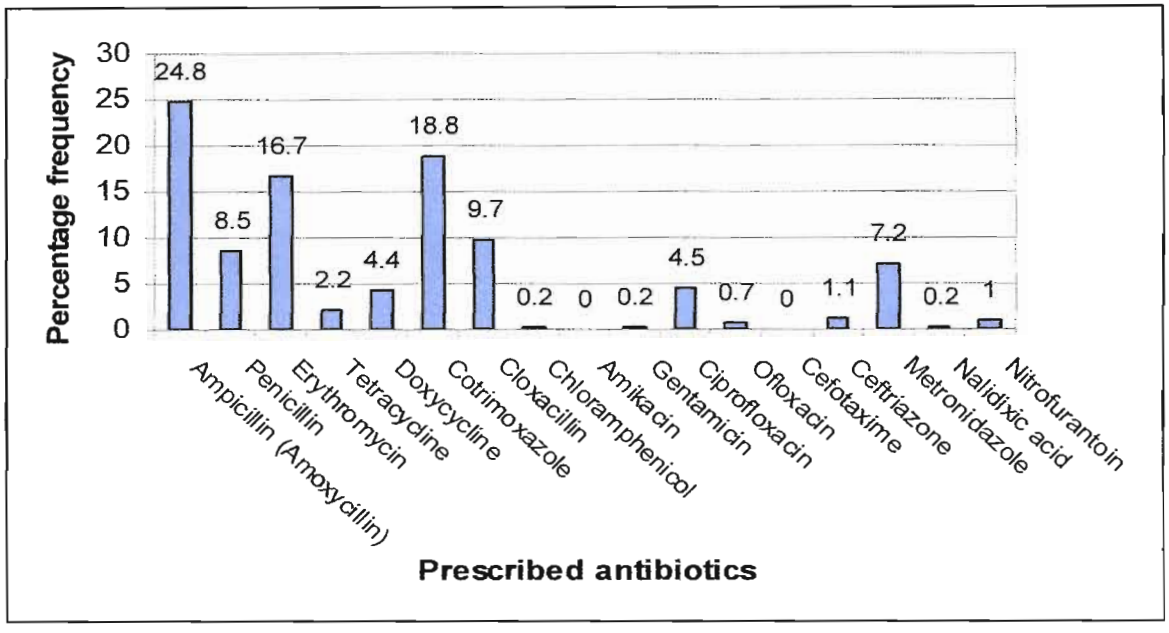

Figure 4.1.12: Percentage frequencies of antibiotic prescribing in outpatient departments at study sites (June 15 -July 15 2006)

- **Rates of prescribed antibiotics for indicated categories of infections**

Analysis of data to indicate the extent to which individual antibiotics were prescribed for *indicated categories* of infections among outpatients is shown in Table 4.1.34. Rates of prescribing of antibiotics as indicated in the table are summarised as follows:

- **Ampicillin, co-trimoxazole, erythromycin** and **penicillin** were prescribed for all indicated categories of infections commonly diagnosed in outpatient departments but mostly for respiratory tract infections. This is in the exception of bone infections where, for the one time that the infection was encountered, erythromycin was observed to be the antibiotic prescribed for its treatment.
- Relative to their rates of prescribing for other infections the four antibiotics (ampicillin, co-trimoxazole, erythromycin and penicillin) were observed respectively to be prescribed for *respiratory tract infections* at highest rates of 47.7%, 57.9%, 46.9% and 43.8%.
- Compared to their indicated rates of prescribing for respiratory tract infections,

- **ampicillin** was prescribed at much lower rates of 12.0% for *skin and soft tissue infections*, 9.1% for *gastrointestinal tract infections*, 7.1% for *genitourinary tract infections*, and 1.9% for *pyrexia of unknown origin*;
- **co-trimoxazole** was prescribed at lower rates of 7.3% for *gastrointestinal infections*, 4.7% each for *genitourinary tract* and *skin and soft tissue infections* and 2.6% for *pyrexia of unknown origin*;
- **erythromycin** was prescribed at lower rates of 23.2%, 5.3%, 4.8% and 0.5% for *genitourinary tract*, *skin and soft tissue*, *gastrointestinal tract* and *bone infections* respectively; and
- **penicillin** was prescribed at lower rates of 18.1% for *skin and soft tissue infections*, 16.2% for *gastrointestinal tract infections* and 3.8% for *genitourinary tract infections*.

- **Cloxacillin** was prescribed principally for *skin and soft tissue infections* and at a rate of 70.0%. It was also seen to be prescribed at comparatively much lower rates of 11.7% for *respiratory tract* and 5.8% for *genitourinary tract infections*.
- **Metronidazole** was prescribed mostly and at nearly equal rates of 34.8% and 31.5% for *genitourinary tract* and *gastrointestinal tract infections*. At comparatively lower rates of 19.1% and 2.2% the antibacterial agent was also observed to be prescribed for *respiratory* and *skin and soft tissue infections*.
- With a prescribing rate of 64.3%, **ciprofloxacin** was observed to be prescribed mainly for *genitourinary tract infections*. At much lower rates of 21.5% and 3.6%, the antibacterial agent was also seen to be prescribed respectively for *respiratory tract and skin and soft tissue infections*.
- **Ofloxacin** was prescribed at rates of 77.8% and 11.1% for genitourinary and respiratory tract infections.
- Prescriptions of **doxycycline** and **tetracycline** were also seen mainly in cases of *genitourinary tract infections* where the two antibiotics were prescribed at respective rates of 50.0% and 48.1% relative to their rates of prescribing with other infections. **Doxycycline** was also prescribed at rates of 18.5%, 5.6% and 1.9% for *respiratory tract, skin and soft tissue* and *gastrointestinal tract infections* and **tetracycline** at rates of 18.5% and 14.8% for *respiratory* and *gastrointestinal infections*.
- **Nitrofurantoin** and **ceftriaxone** were prescribed principally in the treatment of *genitourinary infections* where both antibiotics were respectively prescribed at rates of 76.9% and 85.7%. Both agents were also prescribed for the treatment of

respiratory tract infections where they were again prescribed at respective rates of 7.7% and 7.1%.

- **Gentamicin** was prescribed for *respiratory tract infections* in two occasions that the antibiotic was observed to be prescribed.
- **Chloramphenicol** was prescribed twice only for *respiratory tract* and *skin and soft tissue infections.*
- **Nalidixic acid** was also observed to be prescribed twice for *genitourinary tract* and *skin* and *soft tissue infections.*
- **Amikacin and cefotaxime** were not seen to be prescribed at any time in the p*atient* group during the study period.

Antibiotics commonly prescribed for indicated infection categories

Table 4.1.34 shows the percentage frequency distribution of prescribed antibiotics according to clinical conditions. In the following section antibiotics most commonly prescribed in treating indicated categories of infections are presented.

- **Respiratory tract infections**

Ampicillin was prescribed at the highest percentage frequency of 30.1%, relative to other antibiotics, for respiratory tract infections. The antibiotic, thus, was the most prescribed antibiotic for these infections. It was followed by co-trimoxazole (27.6%), erythromycin (19.8%) and penicillin (9.4%). Other antibiotics seen to be seldom prescribed for respiratory infections included metronidazole (3.5%), cloxacillin (2.9%), ciprofloxacin (2.5%), doxycycline (2.0%), tetracycline (1.0%), gentamicin (0.4%), ceftriaxone (0.2%), and chloramphenicol (0.2%) and nitrofurantoin (0.2%).

- **Genitourinary tract infections**

Erythromycin, doxycycline/tetracycline and ciprofloxacin were prescribed at almost the same relative frequencies of (21.0%), (17.4%) and (15.7%) for genitourinary tract infections. These antibiotics together are considered as the most frequently prescribed antibiotics in treating genitourinary tract infections. Other antibiotics seen to be prescribed for the infection included metronidazole (13.5%), ampicillin (9.6%), co-trimoxazole (4.8%), ceftriaxone (5.2%), nitrofurantoin (4.4%), and cloxacillin (3.1%), penicillin (1.7), and nalidixic acid (0.4%).

Table 4.1.34 Percentage frequency distribution of prescribed antibiotics according to clinical conditions - **ALL RECORDS (OUTPATIENT DEPARTMENT**

Diagnosis	Frequencies of prescribed antibiotics according to clinical conditions																	
	Ampicillin/ Amoxycillin		Penicillin		Erythromycin		Tetracycline		Doxycycline		Co-trimoxazole		Cloxacillin		Chloram-phenicol		Amikacin	
	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
Respiratory tract infections	147	47.7 (30.1)	46	43.8 (9.4)	97	46.9 (19.8)	5	18.5 (1.0)	10	18.5 (2.0)	135	57.9 (27.6)	14	11.7 (2.9)	1	50 (0.2)	0	0.0 (0.0)
Gastrointestinal tract infections	28	9.1 (26.4)	17	16.2 (16.0)	10	4.8 (9.4)	4	14.8 (3.8)	1	1.9 (0.9)	17	7.3 (16.0)	1	0.8 (0.9)	0	0.0 (0.0)	0	0.0 (0.0)
Genitourinary infections	22	7.1 (9.6)	4	3.8 (1.7)	48	23.2 (21.0)	13	48.1 (5.7)	27	50.0 (11.8)	11	4.7 (4.8)	7	5.8 (3.1	0	0.0 (0.0)	0	0.0 (0.0)
Skin & soft tissue infections	37	12.0 (21.4)	19	18.1 (11.0)	11	5.3 (6.4)	2	7.4 (1.2)	3	5.6 (1.7)	11	4.7 (6.4)	84	70.0 (48.6)	1	50 (0.6)	0	0.0 (0.0)
Bone infections	0	0.0 (0.0)	0	0.0 (0.0)	1	0.5 (100)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)
Pyrexia with unknown origin	7	2.3 (41.2)	1	0.0 (1.0)	3	1.4 (17.6)	0	0.0 (0.0)	0	0.0 (0.0)	6	2.6 (35.3)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)
Non-bacterial aetiology	67	21.8 (29.6)	18	17.1 (8.0)	37	17.9 (16.4)	3	11.1 (1.3)	13	24.1 (5.8)	53	22.7 (23.5)	14	11.7 (6.2)	0	0.0 (0.0)	0	0.0 (0.0)
Total	**308**	**100 (24.8)**	**105**	**100 (8.5)**	**207**	**100 (16.7)**	**27**	**100 (2.2)**	**54**	**100 (4.4)**	**233**	**100 (18.8)**	**120**	**100 (9.7)**	**2**	**100 (0.2)**	**0**	**0.0 (0.0)**

Table 4.1 .34 (Continued)

Diagnosis	Frequencies of prescribed antibiotics according to clinical conditions																	
	Gentamicin		Ciprofloxacin		Ofloxacin		Cefotaxime		Ceftriaxone		Metronidazole		Nalidixic acid		Nitrofurantoin		**Total**	
	n	**n%**	**n**	**n%**	**n**	**n%**	**n**	**n%**	**n**	**n%**	**n**	**n%**	**n**	**n%**	**n**	**n%**	**n**	**n%**
Respiratory tract infections	2	100 (0.4)	12	21.5 (2.5)	1	11.1 (0.2)	0	0.0 (0.0)	1	7.1 (0.2)	17	19.1 (3.5)	0	0.0 (0.0)	1	7.7 (0.2)	**489**	**39.4 (100)**
Gastrointestinal tract infections	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	28	31.5 (26.4)	0	0.0 (0.0)	0	0.0 (0.0)	**106**	**8.5 (100)**
Genitourinary infections	0	0.0 (0.0)	36	64.3 (15.7)	7	77.8 (3.1)	0	0.0 (0.0)	12	85.7 (5.2)	31	34.8 (13.5)	1	33.3 (0.4)	10	76.9 (4.4)	**229**	**18.5 (100)**
Skin and soft tissue infections	0	0.0 (0.0)	2	3.6 (1.2)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	2	2.2 (1.2)	1	33.3 (0.6)	0	0.0 (0.0)	**173**	**13.9 (100)**
Bone infections	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	**1**	**0.1 (100)**
Pyrexia with unknown origin	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	**17**	**1.4 (100)**
Non-bacterial aetiology	0	0.0 (0.0)	6	10.7 (2.7)	1	11.1 (0.4)	0	0.0 (0.0)	1	7.1 (0.4)	11	12.4 (6.4)	1	33.3 (0.4)	2	15.4 (0.9)	**226**	**18.2 (100)**
Total	**2**	**100 (0.2)**	**56**	**100 (4.5)**	**9**	**100 (0.7)**	**0**	**0.0 (0.0)**	**14**	**100 (1.1)**	**89**	**100 (7.2)**	**3**	**100 (0.2)**	**13**	**100 (1.0)**	**1241**	**100 (100)**

Notations: n% value in bracket determinations based on row totals
n% value **not** in bracket determinations based on column totals

Skin and soft tissue infections

Prescribed at a rate of 48.6% relative to other antibiotics, cloxacillin was the most frequently prescribed antibiotic in treating skin and soft tissue infections among outpatients. It was followed with their indicated frequencies of prescribing by ampicillin (21.4%), penicillin (11.0%), erythromycin and co-trimoxazole (6.4%). Other antibiotics seen to be rarely prescribed for the infection included doxycycline (1.7%) ciprofloxacin and metronidazole (1.2%) and chloramphenicol and nalidixic acid (0.6%).

- **Gastrointestinal and mouth infections**

Metronidazole (26.4%), ampicillin (26.4%), penicillin (16.0%), co-trimoxazole (16.0%), were seen as the major antibiotics prescribed in the treatment of gastrointestinal and mouth infections in outpatient departments. Other prescribed antibiotics for the infection were erythromycin (9.4%), tetracycline (3.8%) and doxycycline and cloxacillin 90.9%)

- **Pyrexia of unknown origin**

Ampicillin, co-trimoxazole and erythromycin were prescribed at respective relative frequencies of 41.2%, 35.3% and 17.6% for pyrexia of unknown origin in outpatient departments and were thus documented as the principal antibiotics used in treating fevers with unidentified causes within the patient group.

- **Bone infections**

Erythromycin was prescribed for the only case of bone infection diagnosed in outpatient departments and may be cited only as an antibiotic most likely to be prescribed for the condition within the patient group.

- **Clinical conditions non-indicative of bacterial infections**

Listed with their indicated relative frequencies of prescribing, ampicillin (29.6%), co-trimoxazole (23.5%), erythromycin (16.4%), cloxacillin (11.2%), penicillin (8.0%), metronidazole (6.4%), cloxacillin (6.2%), doxycycline (5.8%) and ciprofloxacin (2.7%), were seen to be antibiotics most routinely prescribed for clinical conditions considered non-indicative of bacterial infections. Other antibiotics observed to be prescribed in such

cases but at much lower frequency rates were tetracycline (1.3%), nitrofurantoin (0.9%) and nalidixic acid (0.4%).

4.1.2.5.2 Results evaluation and discussion

- **Rationale and essence of categorising diagnosed infections into categories of their anatomical sites of origin**

Knowledge of the type and antibiotic sensitivity characteristics of bacterial pathogens involved in an infection is a requirement in selecting antibiotics for the effective treatment of infections. In clinical practices in which antibiotics are empirically prescribed, this necessitates that a prescriber make a near correct decision on what bacterial pathogens are likely to be involved in the infection being treated to be able to select such antibiotics. Deciding correctly on pathogenic bacteria implicated in the infection in principle must be based on precise diagnosis of the infection resulting from meticulous diagnostic workups that evaluate among other things, presenting signs and symptoms of the infection in relation to its anatomical site of origin.

Bacterial pathogens have differing microbial surface structures that serve as different virulence factors which enable them to attach to host tissues as they colonise and invade said tissues (Elliot *et al.*, 2004: 6). In addition to this and according to Piers (2005:702), pathogens have varying nutrient requirements as well as local conditions of temperature, pH and oxygen availability for their growth. Pathogens whose growth needs are met in a given tissue where they colonise, for these reasons, will thrive and cause disease in the host. Also, a pathogen that colonises and grows in a given environment in the host must be able to avoid host defence mechanisms militating against its invasion of the host tissue to be able to cause disease in the host. Staphylococci are more capable than other bacterial pathogens for example, to tolerate the harsh conditions of the skin and hence more easily infects tissues of this anatomical site to cause disease in human hosts (Piers, 2005:702) (Detailed literature review on mechanisms of bacterial pathogenesis provided in Chapter 2, Section 2.1.3).

By reasons of their possession of different virulent factors, nutrient requirements for growth and mechanisms of host defence system avoidance, bacterial pathogens have different capabilities of invading and causing disease in different tissues of various anatomical sites of the body. They have for these reasons, varying chances of causing

infection at these sites. It logically follows from this that for given diagnosed infections at given anatomical sites there would be pathogens with specific pathogenic characteristics that would have higher chances than others of being implicated as causative agents of such diagnosed infections at the given anatomical sites. Knowledge of pathogens with higher chances of causing infections at given anatomical sites provides a means of making near correct guesses of pathogens most likely to be implicated in infections at a given anatomical site and hence the selection of antibiotics for their appropriate targeting in the empiric treatment of those infections.

Guglielmo (2009:56-1) acknowledged this when he indicated the establishment of the presence and site of an infection as important factors in directing therapy against pathogens implicated in infections. Based on these considerations, diagnosed infections have been grouped and indicated as infections of respective anatomical sites. This has the purpose of associating groups of pathogens most likely to be involved in diagnosed infections of such sites to allow for effectiveness evaluations of antibiotics commonly prescribed in treating such infections.

Precise diagnosis of infections is paramount to the effectiveness and hence the appropriateness of empirically prescribed antibiotics in treating diagnosed infections of indicated anatomical sites. The relevance of this becomes more important when it is considered that diagnosed infections involving a given anatomical site may not necessarily have bacterial aetiologies. According to Gonzales *et al.* (2001: 493), symptoms of infections with bacterial, viral and even fungal aetiologies at certain anatomical sites do have similarities that can complicate and create doubts in the effectiveness of antibiotic treatment of such infections if such treatments are based on the presence of symptoms alone without a diagnostic workout that would differentiate possible causative agents of the infection in question.

- **Evaluations of prescriber diagnosed infections indicated as basis for antibiotic prescriptions**

A number of diagnoses, symptoms and symptom complexes prescribers indicate as signifying bacterial infections to justify their prescription of antibiotics in outpatient departments are known by literature findings, (Gonzales *et al.,* 2001: 493), as either not being absolute for or not of bacterial aetiologies. In the case of respiratory tract infections prescribers indicated, among others, diagnoses of "upper respiratory tract

infections", pharyngitis, laryngitis, tonsillitis and bronchitis as infections of the respiratory tract for which they prescribed antibiotics (Table 4.1.29). As references cited in Appendix 6 indicate these infections are not of absolute bacterial aetiologies. According to Hart (2007:608), these infections, generally described as acute respiratory infections and seen principally in primary health care settings (outpatient departments) are mainly of viral aetiologies with less than 2% of cases stemming from bacteria. Prescribers also indicated such terms as "respiratory tract infections" without indications of whether they are infections of the lower or upper respiratory tract. They also used frequently symptoms of cough (often without descriptions of the nature of cough or with descriptions non-indicative of bacterial infections of the respiratory tract), chest pain, shortness of breath and nasal congestion to indicate infections of the respiratory tract for which they prescribed antibiotics. While the use of such terms as "upper respiratory infections" pharyngitis, laryngitis, tonsilitis and bronchitis are definitive and suggestive of precise diagnoses with known aetiologies, the use of terms such as "respiratory tract infections" and of symptoms as indicated above, do not define particular diagnoses.

In diagnosed cases of urinary tract infections (UTI) prescribers also indicated terms such as "burning on micturition", dysuria, "hot urine" or "bloody or coloured urine" or simply "urinary tract infection" as their diagnosis of uncomplicated UTI. Indications of such specific diagnoses as urethritis and cystitis (lower respiratory tract infections) pyelonephritis, prostatitis, intrarenal and perinephric abscesses (upper urinary tract infections) had not been noticeably used by prescribers to indicate their diagnosis of infections of the urinary tract. Stamm (2005:1717) listed dysuria, urinary frequency and urgency on one hand and suprapubic pain on the other, as symptoms patients will report when they have cystitis. Fish (2008:64-3) in addition to these indicated also "burning on urination" "blood in urine" and "back pain" as other cardinal symptoms suggestive of lower or uncomplicated UTI. By these literature references, prescribers' use of these diagnostic terms suggests their seemingly "adequate" diagnosis of these infections. This said, however, it is noted that dysuria or burning on micturition and urinary frequency as prescribers variously used as diagnosis for UTI, may also be caused by sexually transmitted pathogens such as *C. trachomatis* and *N gonorrhoea* (Stamm, 2005:1717) and not only by known uropathogens e.g. *E. coli, Klebsiella, Proteus* or *Staphylococcus saprophyticus* (Stamm, 2005:1715). Also, patients with acute pyelonephritis according to Stamm (2005:1715) may demonstrate symptoms of cystitis as well as haematuria.

Stamm (2005:1715) such patients may characteristically show rapid onset of symptoms such as fever, shaking chills, nausea, vomiting and diarrhoea. For reasons of these symptoms as used in the diagnosis of uncomplicated UTI also manifesting as other types of infections of the urinary tract, the use of the terms as diagnoses of UTI may be seen as inconclusive. It does not provide convincing evidence of prescribers' differential diagnosis of the infection to establish definite cases of lower UTI e.g. cystitis or upper UTI e.g. pyelonephritis. Using such precise diagnostic terms as cystitis or pyelonephritis to indicate infections of the urinary tract, for example, connotes differential diagnosis of infections of the tract and the provision of more tailored treatment options of the respective types of UTI. Cystitis and pyelonephritis as two different diagnoses of lower and upper UTI are treated differently (Stamm, 2005:1719). While the former may need a 3-day course of antibiotic treatment to resolve according to the author, the latter may require a 7 - 14 day course of same antibiotic treatment. These considerations underscore the need to accurately diagnose the infection before treatment is attempted. This, by results of this study, was not seen to be done.

Vaginal and penile discharges had been largely used as diagnosis of infections of the genitourinary tract and treated as such. They were most often not described. When described, indications were made of such discharges being profuse, purulent with offensive smell, yellow, white or clear. Vaginal or penile discharges with such descriptions are often indicative of infections by sexually transmitted pathogens that may include *N. gonorrhoea* or *C. trachomatis* (Ram & Rice, 2005:857) or *Trichomonas vaginalis* (Weller, 2005:1252). Prescribers also used terms like "sexually transmitted infections" or vaginitis to indicate the infections. In all instances of such diagnoses a syndromic approach involving the use of multiple antibacterial agents to cover all possible pathogens was adapted in the treatment of the infections. Prescribers' use of diagnostic terms to establish these infections has for these reasons been considered adequate. Prescriber indications of vaginal candidiasis, herpetic genital ulcers and vaginal itches with no discharges or odour as diagnoses or symptomatic descriptions of genitourinary tract infections are not of bacterial aetiologies and may not need antibiotic treatments as observed to be currently done by results of this study. Diagnoses of infections of the tract such as orchitis, vaginal lesions or ulcers may be of possible bacterial aetiologies only (Appendix 6) and may need more precise diagnostic workups to establish their bacterial aetiologies.

In the case of gastrointestinal and mouth infections, prescriber indicated diagnoses of gastritis, gastroenteritis (symptomatically indicated as diarrhoea in some instances), abdominal pain mouth ulcers and parotiditis are diagnoses which may or may not be of bacterial aetiologies (Appendix 6). Similarly while prescriber diagnoses of seborrhoea and scabies are by literature findings absolutely not of bacterial aetiologies in the case of skin and soft tissue infections, diagnoses of skin rashes, panniculitis and conjunctivitis may or may not be of bacterial aetiologies (Appendix 6).

Respiratory tract infections diagnosed and indicated by terms that were not absolute for bacterial infections of the tract represent 85.2% of all diagnosed cases (n = 440) of the infection (Table 4.1.29). By calculation this gave 50.8% of total 865 antibiotic prescriptions assessed for outpatient department. In the case of gastrointestinal tract, conditions diagnosed and indicated by the terms gastritis, gastroenteritis, abdominal pain, mouth ulcers and parotiditis as indicated above are infections with possible bacterial aetiologies (Appendix 6). They represent 74.6% of all cases of gastrointestinal diseases (n = 75) diagnosed as infections (Table 4.1.31) which by calculation gave an equivalent 6.5% (56 out of 865) as the percentage of total antibiotic prescriptions assessed for outpatient departments. Similarly 24.9% of total cases of diagnosed skin and soft tissue conditions (n = 155) treated with regular antibiotics were indicated by diagnostic terms non-indicative of bacterial infections or were indicative of bacterial infections that are uniquely treated with specific antibiotic treatment protocols, They constitute 3.9% of total antibiotic prescriptions assessed for outpatient department and include diagnoses of dermatological conditions indicated as insect bites, skin rashes, seborrhoea and scabies which are non-indicative of bacterial infections or leprosy (Table 4.1.32). Leprosy is an infection of *Mycobacterium leprae* that is uniquely treated with regimens of dapsone or rifampicin or their combinations for many years (Gelber, 2005:966 & 971).

From the above results evaluations, percentage frequencies of indications of prescriber diagnosed infections described with diagnostic terms or symptoms unspecific for bacterial infections in total were found to constitute 61.2% of the total 865 antibiotic prescriptions assessed for outpatient departments. Prescribers, by interpretations of the results of this analysis, were largely seen as not to sufficiently diagnose presenting

cases of infections in outpatient departments to establish their aetiological agents before treating them as bacterial infections. The high percentages of 85.2% and 74.6% of the total number of cases of respiratory and gastrointestinal infections observed to be described with diagnostic terms or symptoms that were not indicative of infections with absolute bacterial aetiologies, evidently categorised these two infections as infection types that were the least sufficiently diagnosed to establish bacterial pathogens as their aetiologies before antibiotics were prescribed. These findings seriously question prescribers' certainty in their diagnosis and hence their expertise in the competent treatment of infections presenting in outpatient settings. Though answers to such questions are beyond the objectives of this study, the problem of possible lack of adequate knowledge in the differential diagnosis and treatment of clinical conditions that may demonstrate similarities with bacterial infections is postulated. The problem is identified as a source of inappropriate prescribing of antibiotics in outpatient settings and the conduction of continuous education seminars for prescribers in the diagnosis and clinical management of such conditions proposed for its solution.

Correlation of infection types with appropriateness of antibiotic prescribing

Prescription assessment results shown in Figure 4.1.8 typically demonstrated 34.6% and 43.8% of the total number of outpatient prescriptions as being prescribed appropriately and respectively for infections with absolute (category A1) or possible (category A2) bacterial aetiologies. This in total gave a majority 78.4% of the total number of prescriptions assessed for outpatient departments of study sites to be observed as being written appropriately in accordance with antibiotic prescribing principles. These results, though indicative of good antibiotic prescribing abilities on the part of prescribers, seemed by explanations given below to be determined more by types of infections seen and treated in outpatient departments than by prescribers' abilities to diagnose and treat infections appropriately.

Reasons for the high percentage of prescriptions in outpatient departments being observed to be appropriately written according to antibiotic prescribing principles had been offered in earlier paragraphs. Most types of infections commonly seen presenting in outpatient settings as indicated, often present with characteristic recognisable signs and symptoms that are associated with infections at given anatomical sites. While such clinical signs may indicate presence of infections at the given anatomical site, they may

not be absolute for bacterial infections always. Respiratory tract infections as cited as an example, are known to have viral aetiologies which present with symptoms difficult to differentiate clinically from infections of the tract caused by bacterial pathogens (Gonzales *et al.*, 2001:491,492). Gastroenteritis with symptoms of diarrhoea similarly may have aetiologies other than bacterial pathogens (Parashar & Glass, 2005:1140; Ahlquist & Camilleri, 2005:226 & 227) while vulvovaginal pruritus, burning or irritation with scanty vaginal discharges which is caused by *Candida albicans* may be diagnosed as genitourinary tract infection and treated with antibiotics (Holmes, 2005:768).

In the absence of diagnostic tests necessary for differentiating absolute bacterial infections from infections with other aetiological agents, empiric antibiotic prescribing for infections in which bacterial pathogens have not been positively identified as causative agents are in fact being done for cases of possible bacterial infections only. Such manner of antibiotic prescribing, though, may seem in principle to be done appropriately in accordance with principles of rational antibiotic prescribing, would not be therapeutically effective in all cases and still constitute a major problem for which prescribers' adherence to principles of prescribing antibacterial agents in the empiric treatment of infections does not appear to offer a solution. As already indicated the conduction of educational seminars or workshops for prescribers in the differential diagnosis and treatment of infections particularly known to be of bacterial and non bacterial aetiologies is proposed as a means of solving the problem. As many studies like those of Hennessy *et al.* (2002:1544,1547) and McNutty *et al.* (2000:497) have shown, education of prescribers on antibiotic prescribing particularly if disseminated through workshops can result in positive alterations of prescribers' antibiotic prescribing practices.

Prevalence of infection types for which antibiotics had been prescribed in this study showed that 47.3% of all outpatient antibiotic prescriptions were given for infections of the respiratory tract and for 16.6%, 15.1% and 8.1% of infections of skin and soft tissues, genitourinary and gastrointestinal tracts (Figure 4.1.11). By results of the study these infections were identified as the main infection types for which antibiotics were prescribed in outpatient departments. Production of pus or abscess formation or inflammation as seen in infections of skin and soft tissue infections (Gerald, 2005:705), complaints of burning sensation or pain on urination, or exudations of mucopurulent or

purulent foul smelling vaginal or urethral discharges (Holmes, 2005:763; Stamm, 2005:1715) are signs and symptoms that glaringly identify bacterial infections of the indicated anatomical sites for which standard antibiotic prescriptions are given. Indeed, apart from certain types of vaginal discharges and genital lesions which may have fungal, protozoa or viral aetiologies signs and symptoms of genitourinary tract infections with bacterial aetiologies are easily identified by the sepsis and foul smells associated with them (Holmes, 2005:768).

Interpreted on the basis of literature documented common aetiologies of upper respiratory tract infections being either of viral or bacterial aetiologies (Gonzales *et al.*, 2001:491,492), the high relative frequency of prescriptions classified as category A2 can be considered as indicative mainly of prescriptions written appropriately according to principles of rational antibiotic prescribing for respiratory tract infections of principally viral and bacterial aetiologies. Similarly prescriptions classified as belonging to category A1 on the basis of the above reasoning are considered to be for skin and soft tissue and genitourinary tract infections. These infections as indicated above are very easily diagnosed as bacterial infections based on their associated signs and symptoms.

The ratio of two numbers X1 and X2 can be written as X1:X2 where X1 and X2 are the first and second terms of the ratio set. For a given ratio, the quotient of the two terms X1 and X2 (i.e. X1/X2) remains constant as X1 and X2 vary. Sets of ratios with the same values for X1/X2 by this argument are equal. By determining and comparing the quotients X1/X2 for given sets of ratios the equality of such sets of ratios can be assessed. Based on this mathematical considerations, the ratios of percentage frequencies of category A1 and category A2 prescriptions (Figure 4.1.8) and the total of percentage frequencies of prescriptions given for skin and soft tissue and genitourinary tract infections (SSI and GUTI) on one hand and the percentage frequencies of respiratory tract infections (RTI) on the other were determined. The quotient of the percentage frequencies of A1 and A2 was determined and so also was that of the total percentage frequencies SSI and GUTI on one hand and the percentage frequency of RTI on the other hand (Table 4.1.2). The calculated values of 0.7 and 0.8 for the two ratio sets compare favourably. This by interpretation, indicates that prescriptions categorised as appropriately prescribed for absolute (category A1) and possible(category A2) bacterial infections were actually prescriptions mostly given for

the respective treatments of SSI and GUTI (compared with category A1) on one hand and RTI (compared with category A2) on the other. Observed differences between percentage frequencies of A1 prescriptions and total prevalence of GUTI and SSI on one hand and also between A2 prescriptions and prevalence of RTI on the other hand could be accounted for by proportions of the respective prescription categories contributed by prescriptions given for other infections. Examples of category A1 and A2 prescriptions as given in treating various infections in outpatient departments of study sites are provided in Table 4.1.36 and Appendix 5.

Table 4.1.35: Calculated ratios of percentage frequencies of category A1 and category A2 prescription; and also of the total percentage frequencies of SSI and GUTI on one hand and RTI on the other.

Indicated prescription categories and	Percentage frequencies and ratios of prescription categories and indicated infections					
	All study sites	Berea	Maluti	Motebang	Queen II	Scott
A1	34.6	12.0	41.o	33.7	32.1	44.2
A2	43.8	64.0	32.3	48.3	44.7	45.5
A1: A2	34.6:43.8	12:64	41:32.3	33.7:48.3	32.1:44.7	44.2:45.5
A1/A2	**0.8**	**0.2**	**1.3**	**0.7**	**0.7**	**1.0**
SSI	16.1	13.0	21.7	10.6	21.6	16.3
GUTI	15.1	0.0	26.8	15.9	14.7	18.8
SSI+GUTI	31.7	13	48.5	26.5	36.3	35.1
RTI	47.3	69.6	39.5	68.9	51.5	60.0
(SSI+GUTI): (RTI)	31.7:47.3	13:69.6	48.5:69.6	26.5:68.9	36.3:51.5	35.1:60.0
SSI+GUTI)/(RTI)	**0.7**	**0.2**	**1.2**	**0.4**	**0.7**	**0.6**

Data Source: Percentage frequencies of prescription categories A1 and A2 - Figures 4.1.8 and 4.1.9.
Percentage frequencies of indicated infections - Figure 4.1.11 and Table 4.1.33

Abbreviations: SSI - Skin and soft tissue infections; GUTI - Gastrointestinal infections; RTI - Respiratory tract infections

Table 4.1.35 also shows for respective study sites calculated ratios with their constants of variations for percentage frequencies of categories A1 and A2 prescriptions (Figure 4.1.9) and the percentage frequencies of GUTI and SSI on one hand and of RTI on the other as diagnosed at respective study sites (Table 4.1.33). Favourable comparisons with 0.0 and 0.1 differences between constants of variations of compared ratio pairs were observed for the Berea, Maluti and Queen II hospitals. By interpretation this indicates as earlier observed, that antibiotics prescribed appropriately for absolute

(category A1) and possible (category A2) bacterial infections at these three study site hospitals, were mostly prescribed for GUTI and SSI on one hand (compared with category A1 prescriptions) and RTI on the hand (compared with category A2 prescriptions). The comparative ratios were less agreeable in the cases of the Motebang and Scott hospitals. Percentage frequencies of diagnosed cases of respiratory tract infections were conspicuously higher than corresponding percentage frequencies of category A2 prescriptions in the cases of the Motebang and Scott hospitals. Similarly, sum totals of percentage frequencies of diagnosed cases of GUTI and SSI were lower than corresponding frequencies of category A1 prescriptions for the two hospitals.

It could be inferred from this trend that more prescriptions of respiratory tract infections were diagnosed as respiratory tract infections with absolute bacterial aetiologies at the Motebang and Scott hospitals than the Berea, Queen II and Maluti hospitals. The observed pattern of percentage frequencies of categories A1 and A2 prescriptions respectively and generally corresponding agreeably with sum totals of prevalence of GUTI and SSI on one hand and of RTI on the other for the majority three study site hospitals confirmed earlier observed documentations that antibiotics prescribed

Table 4.1.36: Examples of appropriately written prescriptions with indicated diagnosis/ symptoms for which they were written

Prescription Record	Diagnosis/Symptoms	Prescribed antibiotics	Appropriateness classification
304-OPD-Maluti	Bronchitis	Erythromycin	A2
513-OPD-QE II	Bronchitis	Amoxycillin	A2
803-OPD- QE II	Cough (no description)	Co-trimoxazole	A2
386-OPD-QE II	Gastroenteritis	Co-trimoxazole Metronidazole	A2
662-OPD-QE II	Urinary tract infection	Nalidixic acid	A1
362-OPD-Maluti	Urinary tract infection + Chest pain +Cough (no description)	Co-trimoxazole Ciprofloxacin Doxycycline Metronidazole	A1
223-OPD-QE II	Skin and soft tissue infection	Cloxacillin	A1
697-OPD-QE II	Urinary tract infections with Orchitis (Genitourinary tract infection)	Metronidazole Ciprofloxacin Tetracycline	A1

appropriately for absolute and possible bacterial infections were indeed prescribed mostly GUTI and SSI on one hand and RTI on the other.

Variations in the extent to which percentage frequencies of indicated prescription categories agree with percentage frequencies of similarly indicated diagnosed infections suggest different levels to which prescribers demonstrate their abilities to differentially diagnose and treat infections of bacterial and non bacterial aetiologies at respective study site hospitals. Prescribers at the Queen II, the Maluti and the Berea hospitals were seen by this results evaluation to demonstrate the same level of competence in differentially diagnosing infections with bacterial and non bacterial aetiologies. Prescribers at the Motebang and Scott hospitals similarly were observed to demonstrate same level of expertise and perhaps more competent in the differential diagnosis of respiratory tract infections than their counterparts at the Queen II and the Maluti hospitals.

- **Epidemiology of diagnosed infections**

More than 50% of all cases of infections either diagnosed as specific diseases or described by symptom complexes were found to be respiratory tract infections. These by results analysis were documented as the leading or most prevalent prescriber diagnosed infection for which antibiotics had been prescribed in outpatient departments. It was followed by skin and soft tissue and genitourinary tract infections, both of which were diagnosed and treated at similar and comparatively much lower relative frequencies of about 18%. The three types of infections together with gastrointestinal tract and mouth infections which were diagnosed and treated at still lower relative frequencies of 9.1%, were identified as the major infections seen and treated in outpatient departments of study sites (Table 4.1.33).

All infections, by indications of their relative frequency distribution within respective study site hospitals were seen to be treated, mostly, at the Queen II hospital followed in that order by Maluti, Motebang, Scott and Berea hospitals. Gastrointestinal tract and mouth infections as an exception to this trend were seen and treated more at the Berea than Scott hospital.

- **Patterns of antibiotic prescribing in Outpatient Departments**

- **Limitations in determining frequencies of prescribed antibiotics**

As indicated in the analysis of inpatient prescriptions, determining rates at which antibiotics were prescribed in the treatment of diagnosed infections is difficult in cases where multiple antibiotics were prescribed in treating concurrently diagnosed infections in patients. In absence of prescriber's indications of which antibiotic they prescribed and for what infection in such instances, the researcher was unable to identify antibiotics that were prescribed for specific diagnosed infections in patients diagnosed with multiple infections and to determine accordingly their frequencies of prescribing for such infections. This generally is a limitation in retrospective drug utilisation study in which prescribers did not indicate specific clinical conditions for which they prescribe given drugs. Since infections can be caused by multiple pathogens and antibiotics similarly can be active against multiple pathogens, each prescribed antibiotic under these circumstances was deemed as prescribed for each of the diagnosed infection. Frequencies of prescribed antibiotics determined this way were however seen to be liable to give inaccurate results in regard to rates of prescribing certain antibiotics for certain infections. In practice, certain antibiotics, the narrow spectrum antibiotics in particular are targeted against certain pathogens and hence prescribed for specific infections. If such antibiotics are considered prescribed for each infection in cases of multiple diagnosed infections, they would be taken in such cases as prescribed for infections for which they are not normally indicated. Their determined frequencies of prescribing for such infections would distort information on their general pattern of prescribing for diagnosed infections. This accordingly would invalidate conclusions drawn based on such determined patterns of their prescribing.

By examining outpatient antibiotic data analysed for the study, the following are listed as typical antibacterial agents that were prescribed in multiple diagnosed infections and whose determined frequencies of prescribing for infections for which they are ordinarily indicated would have to be interpreted with caution. They include metronidazole which is indicated for anaerobic and protozoal infections; cloxacillin which is recommended mainly in the treatment of skin and soft tissue infections (SSI) with staphylococci as implicating agents; ciprofloxacin which also is recommended mainly in the treatment of genitourinary tract infections and gram negative bacilli infections and nalidixic acid which

is also commonly prescribed for urinary tract infections (UTI) . Typical instances in which they were observed to be prescribed with other antibiotics in the treatment of multiple infections and their frequencies of prescribing in such instances included:

- Six cases in which **cloxacillin** was prescribed with ampicillin or penicillin or erythromycin in treating SSI diagnosed concurrently with respiratory tract infections (RTI) [Patient record nos. 481OPD (Queen II) and 511 OPD(Queen II) 567OPD (Queen II), 252OPD (Scott) and 73OPD (Motebang)] and with otitis media (Patient record no. 480OPD (Queen II);
- Seven cases in which **metronidazole** was prescribed with ampicillin and or erythromycin or co-trimoxazole in the treatment of genitourinary tract infections (GUTI) diagnosed concurrently with RTI or prescribed with tetracycline and ampicillin in treating GUTI diagnosed concurrently with gastroenteritis
- Six cases in which **ciprofloxacin** was prescribed with ampicillin and/or erythromycin co-trimoxazole or prescribed with metronidazole in the treatment of GUTI diagnosed concurrently with RTI
- One case in which **nalidixic acid** was prescribed with ampicillin in the treatment of UTI and skin and soft tissue infections (Patient record no. 302 OPD (Queen II).

- **Patterns of antibiotic prescribing**

A majority 39.4% of total antibiotics given for the treatment of variously diagnosed cases of infections were given for *respiratory tract infections* (Table 4.1.34). This establishes the infection type as the one category of infections for which antibiotics were most frequently prescribed. It was followed in that order by *skin and soft tissue*, *genitourinary tract* and *gastrointestinal tract and mouth infections*. Prescribers' choice of antibiotics in treating these infections in order of decreasing frequencies at which they were prescribed as results further indicated were

- *Respiratory tract infections*: **ampicillin, co-trimoxazole, erythromycin,** and **penicillin**, with rates of their prescription varying from between 9.4%% for penicillin to 30.1% for ampicillin (Table 4.1.34).
- *Skin and soft tissue infections*: **cloxacillin, ampicillin, penicillin, erythromycin** and **co-trimoxazole**. With relative rates of their prescription of between 6.4% for co-trimoxazole to 48.6%% for cloxacillin these antibiotics were seen as the most frequently prescribed antibiotics for the infection categories (Table 4.1.34).

- *Genitourinary tract infections*: **Erythromycin, ciprofloxacin, metronidazole, doxycycline/tetracycline, ampicillin/amoxycillin, co-trimoxazole** also with relative rates of prescription of between 4.8% for co-trimoxazole to 21.0% for erythromycin are considered as the most frequently prescribed antibiotics in treating genitourinary tract infections (Table 4.1.34).
- *Gastrointestinal tract and mouth infections* were seen to be treated preferably with **metronidazole, ampicillin, penicillin, co-trimoxazole** and **erythromycin** in that order. With rates of their prescription ranging from between 9.4% for erythromycin to 26.4% for ampicillin and metronidazole, these antibiotics were identified as the most frequently prescribed antibiotics for the infection type (Table 4.1.34).

- **Effectiveness evaluations of prescribed antibiotics in outpatient departments.**

In the assumption that antibiotics are prescribed in circumstances where presence of bacterial pathogens as aetiological agents of infections have been absolutely established, expected outcomes of such treatments would be seen to depend on how effectively prescribed antibiotics eradicate offending pathogens. It follows then that for best treatment outcomes to be achieved in the treatment of infectious diseases, it is imperative for antibiotic choices to be made based on knowledge of both the disease causing pathogen(s) and their sensitivity patterns to prescribed antibiotics. Patterns of antibiotic prescribing in outpatient departments, as results show, demonstrate a trend in which particular antibiotics are routinely prescribed for the empiric treatment of infections at given anatomical sites. While such patterns of antibiotic prescribing may be based on prescribers' knowledge of bacterial pathogens associated with infections at the given anatomical sites, the effectiveness of prescribed antibiotics may still be in doubt in absence of prescribers' knowledge of local antibiotic sensitivity patterns of infecting pathogens. For purposes of providing baseline information required for the effective treatment of infections, it is thought worthwhile to evaluate the effectiveness of antibiotics routinely prescribed for given infections as determined by current antibiotic sensitivity patterns of pathogens associated with infections commonly seen and treated in outpatient departments.

Most probable bacterial pathogens associated with diagnosed infections in outpatient departments had been determined by modifying lists of pathogens found by this study as associated with indicated infections among inpatients. The reason for and the theoretical

basis of modifications are provided in Section 4.1.2.3.2. The lists as generated for the various infections are also provided in Section 4.1.2.3.2. They are repeated in this discussion for the indicated infections for purposes of providing a basis for readers' understanding of the evaluations. Where found necessary brief justifications for the inclusion of certain pathogens in the list of pathogens associated with indicated infections were also made based on literature-derived information.

Percentage overall activities (POA) of antibiotics against pathogens associated with indicated infections as determined and tabulated in Appendices 12(i) through to 12(xiv) were used as basis for evaluating the effectiveness of prescribed antibiotics in treating indicated infections. Where such POA determinations were not possible, the percentage activities (PAs) of antibiotics against pathogens as tabulated in Tables 4.2.4 and 4.2.5 have been used preferentially. Data on bacterial isolates from specimens taken from sites of gastrointestinal infections are not available for this study. In evaluating effectiveness of antibiotics prescribed in treating the infections therefore, pathogens associated with infections of the tract as derived from literature were presumed to be pathogens associated with infections in the local population.

- **Respiratory tract infections (RTI)**

Pathogens presumed to be commonly associated with respiratory tract infections in outpatients as determined and listed in Section 4.1.2.3.2 include both cocci and gram-negative bacilli. They are *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Staphylococcus aureus*, *Staphylococcus epidermidis* (cocci) and *Klebsiella* and *Haemophillus influenzae* (Gram-negative bacilli). Based on determined POAs (or PAs where deemed more appropriate) of prescribed antibiotics against these pathogens the following evaluations are made on the effectiveness of commonly prescribed antibiotics in treating respiratory tract infections in outpatient departments:

- Ampicillin and co-trimoxazole, the first and second most frequently prescribed antibiotics in respiratory tract infections demonstrated POAs of 52% and 42% against pathogens most likely implicated in infections of the respiratory tract among communal patients. The less commonly prescribed antibiotics for the infection, ciprofloxacin, doxycycline/tetracycline, third generation cephalosporins (TGCs) and chloramphenicol on the other hand showed POAs of 78%, 51%, 69% and 65%

respectively against most common pathogens associated with the infection in the patient group [Appendix 12(v)]. Ciprofloxacin, shows moderate activity only against streptococci and is not recommended for use in treating pneumococcal infections of the respiratory tract (British Medical Association and Royal Pharmaceutical Society of Great Britain, 2003:294),

- For throat infections, ampicillin, penicillin, erythromycin, co-trimoxazole and cloxacillin similarly showed POAs of 71%, 53%, 65%, 38% and 65% against most commonly associated pathogens [Appendix 12(vi)]. Ciprofloxacin, TGCs, chloramphenicol, and tetracycline as other antibiotics seen to be prescribed for respiratory tract infections showed POAs of 89%, 81%, 67% and 55% against the spectrum of associated pathogens identified for the infection in outpatients [Appendix 12(vi)].

The above indicated POAs of antibiotics observed to be most commonly prescribed against pathogens most commonly associated with respiratory tract infections in outpatients showed that with current local bacterial pathogen antibiotic sensitivity patterns,

- ampicillin and co-trimoxazole by prediction had low treatment success rates (TSR) when used in treating respiratory tract infections in outpatients.
- in comparison with penicillin and erythromycin, ampicillin was predicted to have higher TSR when empirically prescribed in treating throat infections in communal patients. Based on its activities against pathogens commonly associated with throat infections, co-trimoxazole among all antibiotics commonly used in treating gram-positive infections has the least chance of being successfully used in treating throat infections [Table 4.2.4; Appendix 12(vii)].
- the use of ampicillin (amoxycillin) and co-trimoxazole in patient groups at high risks of developing gram-negative bacterial infections of the respiratory tract, (i.e. elderly patients, patients with bronchiectasis, patients with previous hospital admission or previous history of corticosteroids) is predicted to have low TSRs when used in treating respiratory tract infections in this patient group. Ampicillin and co-trimoxazole, had activities of between 16% and 35.4% against *Escherichia coli* (Table 4.2.5); and

- ciprofloxacin, TGCs, cloxacillin and chloramphenicol in that order were predicted to have higher TSRs when used in treating respiratory tract infections including throat infections among outpatients.

- **Genitourinary tract infections**

In the ensuing discussions the term "urinary tract infections" (UTI) and "genitourinary tract infections" (GUTI) have been used at instances respectively to indicate infections of the urinary tract and concurrent urinary tract infections and vaginal and penile discharges. Urinary tract infections have also been described as uncomplicated infections of the urinary tract and genitourinary tract infections considered as urinary tract infections complicated with infections at other sites of the genitalia. The distinction is made in view of differences in the spectra of pathogens associated with and hence treatment options available for the two infections. Infections diagnosed as sexually transmitted diseases (STD) or cervicitis (vaginal discharges) or urethritis (penile discharges) without indications of any concurrent diagnosis of infections of the urinary tract were not considered in these discussions. STDs have standard antibiotic treatment protocols in Lesotho and have not been considered a problem area worth investigating in this study in regard to antibiotic selections in their empiric treatment.

Pathogens presumed to be associated locally with genitourinary tract infections as determined and listed in Section 4.1.2.3.2 included *Escherichia coli*, *Klebsiella* spp, *Proteus* spp; *Staphylococcus aureus, Staphylococcus epidermidis,* α-haemolytic streptococci (*S. pneumoniae*), non-haemolytic streptococci (non enterococci), β-haemolytic streptococci (*S. pyogenes*), *Neisseria gonorrhoea*.

The list excluded *Pseudomonas* spp as normal pathogens associated with communal genitourinary infections for reasons provided in Section 4.1.2.3.2. Though mostly associated with hospital infections, *Pseudomonas* is also known to cause community acquired infections in immunocompromised patients including debilitated patients and patients with AIDS, (Ohl & Pollack, 2005:893). With a rate of HIV infection and AIDS development in Lesotho at 24% (Ministry of Health & Social Welfare, 2004: 233), there is a likely hood of *Pseudomonas* infections to becoming prevalent in patient groups from communal environments. In spite of it not being presented as part of this study, results of analysing urine specimens collected from outpatients presenting with urinary tract

infections at study sites for their microbial composition during the study period revealed *Pseudomonas aeruginosa,* as a significant pathogen associated with communal urinary tract infections. The organism demonstrated an 8% rate of isolation from the specimens (Figure 4.1.13).

This result showed pseudomonas as an emerging pathogen associated with urinary tract infections among communal populations in Lesotho. Considering patients with HIV infection or AIDS as high risk patients in the development of pseudomonas infections and also considering the fact that *Pseudomonas aeruginosa* had actually been isolated at significant rates in outpatient populations with urinary tract infections (Fig 4.1.13), it is deemed necessary to target pseudomonas in the empiric treatment of urinary tract infections among outpatient populations. This is suggested particularly in cases of recurrent urinary tract infections or in patient groups with known positive HIV status. ,*Pseudomonas aeruginosa* infections exhibit a propensity for persistence, chronicity and recurrence (Ohl & Pollack, 2005:892) as like enterococcus spp which similarly are known common causes of chronic and recurrent urinary tract infections (Shankar *et al.*, 2001:4366).

In GUTI a strong presence of staphylococci (*Staphylococcus aureus* and *Staphylococcus epidermidis*) had been noted, contrary to literature findings. While these may be suggestive of the pathogens being associated pathogens with GUTI in the local population, their presence in urethral and vaginal discharge specimens could also be explained by their being contaminants of thee specimens. Further studies are required to establish their implications in GUTI before the coverage in antibiotic treatments of these infections are considered.

List of pathogens associated with UTI and GUTI among inpatients as determined from results of analysis of urine specimens and specimens of high vaginal or penile swabs (Section 4.2.2, Table 4.2.2) had been modified and extrapolated to reflect pathogens associated with UTI and GUTI among outpatients (Section 4.1.2.3.2). By consideration of this list and also considerations given to pseudomonas as emerging urinary pathogens among outpatient populations as indicated above, uncomplicated UTI or GUTI can be presumed to be associated with the following pathogens among outpatients. They include,

- **UTI**: *Escherichia coli, Klebsiella* spp, *Proteus* spp *Pseudomonas* spp, and *Streptococcus pyogenes* ; and
- **GUTI**: *Escherichia coli, Klebsiella* spp, *Proteus* spp, *Pseudomonas* spp, and *Streptococci pyogenes*. *Staphylococci (*Staphylococcus aureus* and *Staphylococcus epidermidis*), *Neisseria gonorrhoea* and *Chlamydia trachomatis*. (* needs further studies to confirm as true pathogens of the infections among the UTI complicated with urethritis and vaginal discharges)

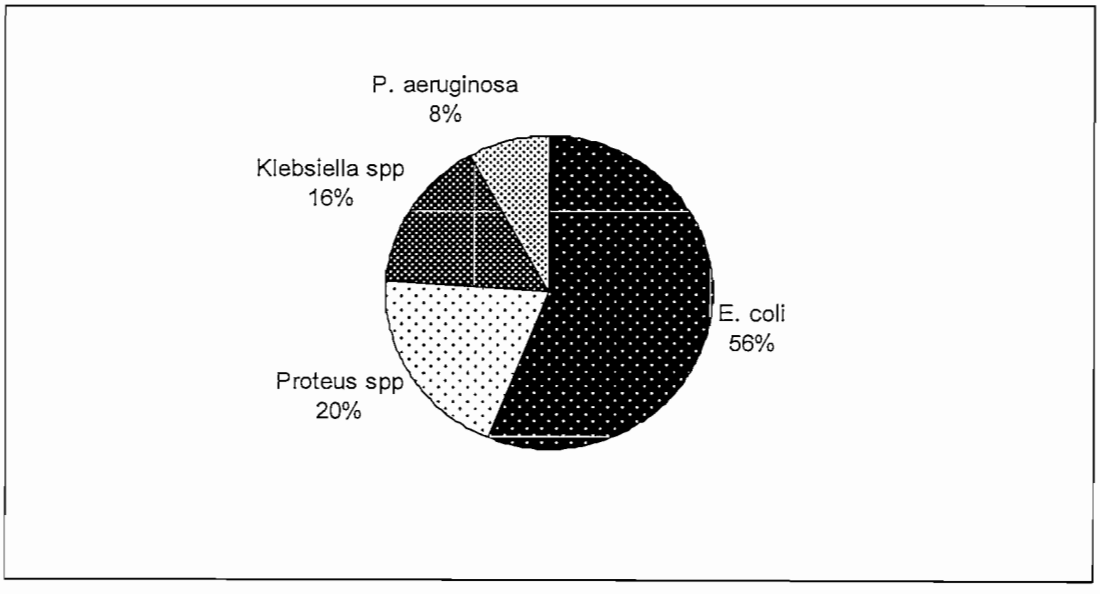

Figure 4.1.13: Percentage frequencies of isolation of bacterial pathogens from urine specimens of communal patients presenting with urinary tract infections at study sites (June 16 to July 31, 2006)

From determined activities or percentage overall activities (POA) or literature information on activities of antibiotics against pathogens associated with UTIs/GUTIs the following are noted:

- **Ciprofloxacin, TGCs** (cefotaxime **ceftriaxone**) and **chloramphenicol** showed POAs of 90%, 93% and 59% against most common pathogens associated with urinary tract infections including *Pseudomonas* spp and enterococci (non-haemolytic streptococci) [Appendix 12(xii)].

- **Ampicillin** and **co-trimoxazole** respectively demonstrate POAs of 18.0% and 34.0% against common bacterial pathogens associated with urinary tract infections excluding *Pseudomonas* [Appendix 12(xiii)] or 19.6% and 32.0% including *Pseudomonas* [Appendix 12(xii)] or 36.0% each against pathogens associated with GUTIs [Appendix 12(xiv)].

- **Nitrofurantoin** and **nalidixic acid**, seen as antibiotics often prescribed for UTI, showed respective percentage activities (PAs) of 86.0% and 81.2% against *Escherichia coli*, 73.0% and 77.4% against *Klebsiella*, 23.0% and 76% against *Proteus*, and 44.0% and 75.0% against *Pseudomonas* (Table 4.2.5). The antibiotics were not tested against gram-positive cocci to allow for determinations of their POAs and hence predictions of their effectiveness in treating UTI in which these pathogens are implicated.

- **Metronidazole**, identified as a commonly prescribed anti-infective agent in the treatment of genitourinary tract infections, is by literature information prescribed mainly for infections of *Trichomonas vaginalis,* protozoa implicated *as* a possible aetiological agent of urethritis or vaginal discharges (Ministry of Health & Social Welfare, 2006: 66). Culture sensitivity test results of pathogens against the antibacterial agent are also not available for use in determining PAs or POAs of the antibacterial agent against bacterial isolates responsible for infections of the urinary tract to enable predictions of its effectiveness in the treatment of infections of the tract caused by other pathogens.

- Reportedly prescribed at same rates of about 18.0% **erythromycin, doxycycline/tetracycline** and **ciprofloxacin** appeared to be prescribed together in the syndromic treatment of genitourinary tract infections (Table 4.1.34). References from Lesotho Standard Treatment Guidelines indicate multiple prescribing of erythromycin (500 mg 6 hourly for 7 days)/ azithromycin (1 gm single dose) orally or

doxycycline (100 mg twice daily for 7 days)/tetracycline (500 mg 6 hourly for 7 days) and ciprofloxacin (500 mg single dose)/ofloxacin (400 mg single dose) orally or ceftriaxone (125 mg IM single dose) for the treatment of urethritis and vaginal discharges (Ministry of Health & Social Welfare, 2006: 65, 66). Also CDC currently recommends treating the urethritis and cervicitis with azithromycin or doxycycline to cover infections of *Chlamydia trachomatis* presumably occurring along with *Neisseria gonorrhoea* as causative agents of the infections and for which the centre recommends cefixime instead of ciprofloxacin in its treatment (Goad & Hess, 2008:65-4). From these treatment recommendations for urethritis or cervicitis, it could be inferred from these recommendations that the three antibiotics - erythromycin, doxycycline/tetracycline and ciprofloxacin - were prescribed solely for cases of sexually transmitted infections demonstrating as penile and vaginal discharges. Also, ciprofloxacin with a recommended dose of 500 mg single dose and erythromycin or doxycycline/tetracycline are noted to be included in the multiple antibiotic therapy to respectively cover *Neisseria gonorrhoea*, and *Chlamydia trachomatis*.

From indicated PAs or POAs of prescribed antibiotics as summarised above those listed below are predicted as treatment outcomes of currently used antibiotic regimens in treating UTIs or UTIs diagnosed concurrent with urethritis or vaginal discharges among outpatients.

- Prescribed in dosage regimens recommended in the treatment of UTI (Butler *et al.,* s.a.:9; Stamm, 2005:1719) **ciprofloxacin and TGCs** have the best chances of successfully treating UTIs empirically.
- Prescriptions of **ampicillin** and **co-trimoxazole** have no benefit in treating UTIs.
- By demonstrating higher PAs against *Pseudomonas, Klebsiella* and *Proteus* nalidixic acid is seen to have higher prospects than nitrofurantoin in the successful empiric treatment of UTIs.
- The higher rates of isolation of *Escherichia coli* in UTI (Table 4.2.2) and the demonstration of a higher PA against the pathogen by nitrofurantoin suggests the use of nalidixic acid as a second choice antibiotic to **nitrofurantoin** in the event of treatment failures with the latter.

- Ciprofloxacin and TGCs demonstrated PAs of 73.0% and 73.1% respectively against *Staphylococcus aureus* and of 83.0% and 69.2% against *Staphylococcus epidermidis* and may be used to appreciable degree in successfully treating infections by these pathogens empirically if employed in long enough dosage regimens (7 - 14 days treatment regimens) as recommended in the literature (Stamm, 2005:1719).

- **Skin and soft tissue infections**

Major skin and soft tissue infections treated in outpatient departments as reported in Table 4.1.31 included abscesses, cellulitis, impetigo, lacerations and bruises, septic ulcers and lesions, skin rashes and animal bites and are similar in the exception of necrotising infections, to skin and soft tissue infections reported in the literature as commonly seen and treated in outpatient clinics (Stevens *et al.*, 2005:1374). These infections by literature findings are associated more with staphylococci (*Staphylococcus aureus* and *Staphylococcus epidermidis* mainly) and streptococci (*Streptococcus pyogenes* mainly) than other bacterial pathogens capable of causing infections of skin and soft tissues (Jones *et al.*, 2003:406; Stevens *et al.*, 2005:1374).

Necrotising infections have largely not been reported as commonly seen infections among outpatients. In the event of their presentations they may be assumed to be associated with the following pathogens as indicated in the literature (Stevens *et al.,* 2005:1375,1384; Bowler *et al.*, 2001: 247). These include Streptococci, (*Streptococcus pyogenes* mainly) or, rarely staphylococci (principally *Staphylococcus aureus*), anaerobic streptococci (*Peptostreptococcus*), *Vibro vulnificus* and *Aeromonas hydrophila* which may be implicated as sole causative agents in monomicrobial infections (Stevens *et al.,* 2005:1375). In polymicrobial necrotising these pathogens may be present together with other streptococci (Group B, C or G streptococci), enteric GNB such as *E. coli* as seen in necrotising fasciitis resulting from penetrating abdominal trauma (Stevens *et al.*, 2005: 1384) or *B. fragilis* group, *P. aeruginosa* as may additionally be encountered in the infections originating from decubitus ulcers (Bowler *et al.*, 2001: 247). In accordance with the above and also from modifications of a list of pathogens associated with skin and soft tissue infections among inpatients as shown in Section 4.1.2.3.2, the following pathogens are presumed to be associated with commonly diagnosed skin and soft tissue infections among outpatients. They include,

- **skin and soft tissue infections [ear infections (otitis externa and otitis media) excluded]:** *Staphylococcus aureus, Staphylococcus epidermidis*, *S. pneumoniae*, *S. pyogenes*, (cocci); and
- **skin and soft tissue infections [ear infections (otitis externa and otitis media) excluded] included):** *Staphylococcus aureus, Staphylococcus epidermidis*, *S. pneumoniae*, *S. pyogenes* (cocci), *Pseudomonas* and *H. influenzae* (gram-negative bacteria associated with ear infections).

Percentage activity considerations of antibiotics observed to be commonly prescribed in skin and soft tissue infections indicated that,

- **Cloxacillin**, the most frequently prescribed antibiotic in skin and soft tissue infections, showed the highest activity of 70% against *Staphylococcus aureus* among all antibiotics tested against gram-positive cocci (Table 4.2.4). The antibiotic also exhibited an appreciable activity of 80% against *Streptococcus pyogenes* but was seen to exhibit low activities of between 50% and 66% against other *Streptococci pneumoniae* and *Staphylococcus epidermidis* which were also observed to be implicated in skin and soft tissue infections. .
- **Ampicillin**, the next popularly prescribed antibiotic in outpatient departments in treating skin and soft tissue infections following cloxacillin, demonstrated a rather low activity of 39.3% against *Staphylococcus aureus*, approximately same activity against *Streptococcus pyogenes* but higher activities than cloxacillin against other gram-positive cocci capable of causing skin and soft tissue infections (Table 4.2.4).
- Local sensitivity patterns of *Streptococcus pyogenes* (<61%), *Staphylococcus aureus* (23.5%) and *Staphylococcus epidermidis* (31.4%) against **penicillin.**
- **Erythromycin** like penicillin demonstrated activities of 60.7% and 67.3% against *Streptococcus pyogenes* (Table 4.2.4).
- **Co-trimoxazole** and **tetracycline** respectively showed activities of between 20.5% to 38.6% and 33.0% to 56.0% against common cocci associated with skin and soft tissue infections (Table 4.2.4) and are not seen as effective in treating skin soft tissue infections.
- **Ciprofloxacin**, **TGCs** were tested for a few times only against staphylococci and streptococci. Though found to demonstrate high activities against these pathogens (Table 4.2.4), the few times of their tests against the pathogens did not provide

sufficient data for analysis and predictions of their effectiveness in treating skin and soft tissue infections.

- **Metronidazole,** also noted to be prescribed in skin and soft tissue infections to cover anaerobic pathogens that might be implicated in some forms of these infections, was not tested routinely against this group of pathogens. No data were as such available for use in evaluating the effectiveness of the antibacterial agent in treating skin and soft tissue infections for which anaerobes may be suspect causative agents.

From indicated PAs of commonly prescribed antibiotics as outlined above the following are inferred as expected treatment outcomes of currently used antibiotic regimens in treating skin and soft tissue infections:

- **Cloxacillin,** despite its exhibition of lower activities against other cocci, demonstrated high activities against *Staphylococcus aureus* and *Streptococcus pyogenes* in comparison with other antibiotics. The antibiotic is, adjudged the most effective antibiotic and hence recommended as a first choice antibiotic for prescription in the empiric treatment of skin and soft tissue infections among outpatients.
- The low activity of **ampicillin** against *Staphylococcus aureus* precludes the use of the antibiotic as a single antibiotic in treating skin and soft tissue infections caused by the pathogen (Table 4.2.4).
- The higher activity of the **ampicillin** against other gram-positive cocci than **cloxacillin,** however, predicts more effective coverage of possible bacterial pathogens associated with skin and soft tissue infections when combinations of the two antibiotics are employed in treating skin and soft tissue infections.
- The demonstration of activities of only 61% and (23.5%) by **penicillin and erythromycin** towards *Streptococcus pyogenes*, *Staphylococcus aureus* and *Staphylococcus epidermidis* predicts unsatisfactory treatment in the use of the antibiotics in treating skin and soft tissue infections (Table 4.2.4). The antibiotics thus may not be prescribed for the empiric treatment of these infections as recommended by Stevens *et al.* (2005:1376).
- The very low activities of **co-trimoxazole** and **tetracycline** against common gram -positive cocci associated with skin and soft tissue infections (Table 4.2.4)

precludes the use of the antibiotics in treating skin and soft tissue infections in contrast the literature's recommendations for their empiric usage (Stevens *et al.*, 2005: 1374).

- **Ciprofloxacin** by literature documentation is only moderately active against gram-positive bacteria and its prescription in the empiric treatment of infections by these pathogens is not recommended (British Medical Association & Royal Pharmaceutical Society: 2003: 294). **TGCs** by a study of Jones *et al.* (2003:408) however, were found to be active against methicillin susceptible strains of *Staphylococcus aureus* (MSSA) and methicillin susceptible coagulase-negative *Staphylococcus aureus* (MS-CNS). Apart from their recommended use in necrotising and animal bite infections to which pathogens other than cocci are associated (Stevens *et al.*, 2005: 1375; Bowler *et al.*, 2001: 247) the use of the antibiotics (ciprofloxacin and TGCs) in treating skin and soft tissue infections is not recommended.
- **Metronidazole,** though not evaluated for its effectiveness against anaerobic bacteria, and as the only antibacterial agent available for treating anaerobic pathogens, could be added to prescribed antibiotics in treating polymicrobial necrotising infections or other forms of skin and soft tissue infections showing presence of anaerobic pathogens. Recognition of such infections to justify the use of the antibacterial agent can be based on characteristics of the infection type as outlined by Kasper (2005: 940, 941). According to the author, malodorous exudates from abscesses give a sign of anaerobic pathogen involvement as causative agents of skin and soft tissue infections. He further stated that infections at sites of tissue necrosis e.g. sites of trauma, tissue destructions and compromised vascular supply where conditions favouring growth, propagation and pathogenesis of anaerobic bacteria exists or infections with abscess that fails to yield organisms on routine culture can be assumed to have anaerobic bacteria as aetiological agents. Such characteristic skin and soft tissue infections can be appropriately treated with anaerobic bacteria as target pathogens.
-

- **Gastrointestinal tract infections**

Culture sensitivity tests have generally not been carried out on specimens from sites of infection of the gastrointestinal tract at study site hospitals. Data for this reason were not

available for analysis to either determine pathogens associated with gastrointestinal infections locally or evaluate effectiveness of antibiotics prescribed in treating the infections based on local activity patterns of such prescribed antibiotics. Pathogens commonly associated with gastrointestinal infections as reviewed from the literature are indicated below. These are presumed to be most likely pathogens associated with respective diagnosed gastrointestinal infections locally. Evaluations of the effectiveness of prescribed antibiotics were done with these as target pathogens. In cases where local PAs of prescribed antibiotics as determined for indicated pathogens were available, these are used in evaluating the effectiveness of such antibiotics in treating infections of the indicated pathogens. In the absence of such PAs, literature-derived information on antibiotic sensitivity patterns of pathogens associated with indicated infections were used in effectiveness evaluations. The presumed pathogens as considered associated with specific infections of the gastrointestinal tract include for the following:,

- **Dental and oral infections**: anaerobic bacteria including *Prevotella spp*, *Porphyromonas spp* and *Fusobacterium* spp (Kasper, 2005:941).
- **Acute gastroenteritis**: *Salmonella* (Lesser & Miller, 2005:901), *Escherichia coli*, *Klebsiella*(Russo, 2005:879&882), enterotoxigenic *Bacteroides fragilis* (Kasper, 2005:943) and *Shigella dysenteriae* (Keusch & Kopecko, 2005:904) and *Yersinia enterocolitica.*
- **Intraabdominal infections**: *B. fragilis* and other anaerobic bacteria including *Clostridium septicum* (Kasper & Zaleznik, 2005: 751&752; Kasper, 2005:943).
- **Bacterial peritonitis:** Gram-negative bacilli e.g. *Escherichia coli* (Russo, 2005:881) and *Enterococcus* spp (Musher, 2005: 830).
- **Appendicitis:** *Yersinia* spp. (Silen, 2005:1805).
- **Anorectal** or **perianal sores**: anaerobic bacteria *Bacteroides, Prevotella, Porphyromonas, Peptostreptococcus* and enteric GNB (Gearhart & Bulkley, 2005:1802).

Penicillin, metronidazole, ampicillin and co-trimoxazole were identified as the most frequently prescribed antibiotics for gastrointestinal infections in outpatient departments (Table 4.1.34). The following were observed in patterns of prescribing the four antibiotics in treating the infections:

- Ampicillin (23.8%) and metronidazole (24.8%) were prescribed at similar rates of 23.8% and 24.8%. This suggests the combined prescribing of the two antibacterial agents in treating gastrointestinal tract infections presumably caused by anaerobic bacteria composed of gram-negative species of the bacteria group.
- Penicillin and co-trimoxazole were prescribed at different rates of 27.7% and 12.9%, showing significant difference in the prescribing rates of the two antibiotics that suggests their being prescribed in the treatment of particular types of gastrointestinal infections.

Ampicillin as prescribed is most probably prescribed together with metronidazole instead of penicillin as recommended in the literature (Elliot 2003: 37; Inglis, 2003: 245; Kasper, 2005:945) in treating mixed infections of the gastrointestinal tract caused by anaerobic and gram-negative bacterial pathogens. Ampicillin and penicillin as Kasper (2005:945) further indicated are intrinsically active against anaerobic bacteria including *Peptococcus*, *Peptostreptococcus*, *Clostridium* and *Propionibacterium* spp. The activity of these organisms against metronidazole on the other hand is unpredictable (Kasper, 2005:945). Anaerobic gram-negative bacilli which are inclusive of *Bacteroides*, *Fusobacterium*, *Prevotella* and *Porphyromonas* are β-lactamse producing. They are sensitive to metronidazole but not ampicillin or penicillin (Ulger *et al.*, 2004:257). Penicillin mono therapy in gastrointestinal infections as the above rating of penicillin prescribing suggests, assume sole infections by gram-positive anaerobic organisms which may not be correct because of the high possibility of mixed infections with both and gram-negative species of anaerobic bacteria occurring together (Kasper, 2005:945). Prescribed in the treatment of gastrointestinal infections, co-trimoxazole may be targeted against gram-negative bacilli either as sole pathogens implicated in the infections or as their mixed infections with other pathogens. Elliot *et al.*, (2004:53) and Russo, (2005:880) recommended the use of the antibacterial agent in treating *E. coli* and *Klebsiella* infections of the gastrointestinal tract while Dennis and Campbell (2005: 928) recommended it in treating *Yersinia enterocolitica* infections of the tract. Local percentage activities of co-trimoxazole against *E. coli* and *Klebsiella* as shown in Table 4.2.5 are respectively 34.5% and 31.7%. These activities are predictive of high failure rates of the use of co-trimoxazole in treating infections of these organisms.

From the above foregoing discussion points the following are inferred as expected or predicted outcomes of current patterns of antibiotic treatment of gastrointestinal intestinal infections:

- The combined prescription of ampicillin and metronidazole in treating mixed infections of and gram-negative anaerobic infections as may occur in dental and mouth infections or intraabdominal infections is predicted to be effective. The recommendation in the literature of the combined use penicillin and metronidazole could, however, be considered a more appropriate choice in the treatment of these infections.
- In view of the noted implication of β-lactamase producing gram-negative anaerobic bacteria in causing dental an mouth infections and intraabdominal infections, the prescribing of penicillin in mono antibiotic therapy of these infections is predicted to be attended with high treatment failures.
- The low activity of co-trimoxazole against GNB and *Yersinia enterocolitica* precludes the use of the antibacterial agent in the empiric treatment of acute gastroenteritis, bacterial peritonitis and anorectal sores where GNB are implicated or in appendicitis where *Yersinia enterocolitica* is the offending pathogen.

- **Recommended antibiotic treatment of gastrointestinal infections**

In the absence of culture sensitivity test results data that could be used in making antibiotic choices for the treatment of gastrointestinal infections, literature recommendations for treating the infections as summarised below have been assessed and used as basis for recommending antibiotics for use in treating gastrointestinal infections.

Infections by anaerobic pathogens are recommended to be treated with penicillin and metronidazole or clindamycin (Kasper, 2005:945). Alternative choices in situations of treatment failures due to resistant organisms as the author further recommended include imipenem, β-lactam antibiotics combined with β-lactamase inhibitors (e.g. ampicillin/sulbactam or amoxycillin/clavulanic acid or ticarcillin/clavulanic acid or piperacillin/tazobactam), chloramphenicol, aminoglycosides and quinolones (Kasper, 2005: 945).

In treating infections by *Shigella dysenteriae and Shigella flexneri*, the quinolones (nalidixic acid or ciprofloxacin) are recommended (Keusch & Kopecko, 2005:905). The antibiotics in addition to the cephalosporins, sulfamethoxazole, aminoglycosides and amoxycillin/clavulanic acid are similarly recommended in the treatment of infections by *Escherichia coli* and *Klebsiella* which also are implicated in gastrointestinal or abdominal infections (Elliot *et al.*, 2004:53, Russo, 2005 880). *Yersinia enterocolitica* isolates produce β-lactamase and are intrinsically resistant to the penicillins and the first and second generation antibiotics. They are usually susceptible to the aminoglycosides, third generation cephalosporins (TGCs), quinolones, chloramphenicol, tetracyclines and co-trimoxazole (Dennis & Campbell, 2005: 928). The fluoroquinolones among these antibiotics, as noted by the authors, exert greatest bactericidal activities against the organisms. Butterton and Calderwood (2005:7590) recommend the use of fluoroquinolones in treating infectious diarrhoea in which *E. coli* is the offending pathogen. Ciprofloxacin is reported to have an activity of 78.0% (Table 4.2.5) against the pathogens and is considered by this study as a preferred choice to co-trimoxazole in treating *E. coli* infections of the gastrointestinal tract.

Taking local bacterial pathogens' antibiotic sensitivity patterns into consideration together with literature recommended antibiotics in the treatment of anaerobic and enteric gram-negative bacilli infections the following formulary antibiotics are recommended for empiric treatment of respective gastrointestinal tract infections:

- Infectious diarrhoea or bacterial dysentery: Ciprofloxacin or Norfloxacin.
- Infectious diarrhoea in which intestinal pathogenic *E. coli* and enterotoxigenic. *Bacteroides* are targeted as offending pathogens: Ciprofloxacin or norfloxacin plus metronidazole.
- Anorectal sores and intraabdominal abscess or appendicitis manifesting as abdominal infections: Penicillin plus metronidazole plus ciprofloxacin.
- Dental and mouth infections: Penicillin or amoxycillin or amoxycillin/clavulanic acid as mono antibiotic therapy regimens.

- **Sources of antibiotic over-prescription in outpatient departments**

Antibiotic prescription in cases of diagnosed infections with non-established bacterial aetiologies

Identified as the major and leading type of infections diagnosed and treated at study site outpatient departments, respiratory tract infections were observed as the one category of infections for which antibiotics are mostly prescribed in outpatient departments at study site hospitals. Up to 86.2% of these infections equivalent to 44.3% of total antibiotic prescriptions assessed for out patient departments as findings of the study further showed infections of the respiratory tract that were not absolute for bacterial infections. Hart, (2007:608) as earlier quoted said these infections manifesting mainly as acute respiratory tract infections are mainly of viral aetiologies with less than 2% of cases stemming from bacteria. Similar to respiratory tract infections, about 74.2% of cases diagnosed as gastrointestinal infections which constituted 5.3% of total prescriptions assessed for outpatient departments of study site hospitals were cases for which bacteria may be considered only as possible aetiologies. Together with percentage of antibiotic prescriptions given for respiratory tract infections with possible bacterial infections, half of total prescriptions given for the treatment of infections can be estimated as prescriptions given for infectious cases for which bacterial pathogens were not established as causative agents. Based on Hart's (2007:608) 2% estimate of acute respiratory tract infections presenting in outpatient settings being infections with bacterial aetiologies, a small percentage only of the estimated half of total antibiotic prescriptions given in treatment of infections for possible bacterial causes can be deduced as actual prescriptions given in treatment of infections that may have bacterial pathogens as aetiologies.

Prescribing antibiotics for cases of infections with non-bacterial aetiologies have by this assessment been identified as a source of antibiotic over-prescribing in outpatient departments. It depicts failure of prescribers to sufficiently diagnose infections and establish their microbial aetiologies before taking decisions to prescribe antibiotics. This is seen as a problem that needs appropriate redress as for example through conduction of education programmes for prescribers, to minimise injudicious use of antibiotics and over come the problem of antibiotic over-prescribing in the country's hospitals.

Antibiotic prescribing for clinical conditions non-indicative of bacterial infections

The prescription of antibiotics in clinical conditions for which uses of antibacterial agents were considered not justified is characteristic of established patterns of antibiotic prescribing in outpatient departments of study sites. Classified as category F prescriptions, examples of such antibiotics given for clinical conditions for which uses of antibacterial agents were considered not justified are provided in Appendix 5 As many as 11.6% of all antibiotics prescribed during the study period as results indicated, were prescribed in this manner (Table 4.1.34). This pattern of antibiotic prescribing is indicative of tendencies on the part of prescribers to prescribe antibiotics in some of the cases either in conditions for which they are not sure of their diagnoses or for reasons other than treating patients' presenting clinical problems. This is confirmed by results of research Phase III Section 4.3.2.

Antibiotics most frequently prescribed for these wrong reasons included in order of their relative frequencies of prescribing in situations when uses of antibiotics in the treatment of presenting clinical conditions were considered not justified include ampicillin, co-trimoxazole, penicillin, erythromycin and cloxacillin. With a cumulative percentage frequency of their prescribing for clinical conditions considered unjustified for antibiotic use determined as 77.6% (Table 4.1.34), these antibiotics evidently constitute antibiotics most over-prescribed or misused in outpatient settings of study sites. True to predictions based on the impact of antibiotic over-use on pathogen antibiotic resistance development, some of these antibiotics by results of research Phase II Section 4.2.3.1 were seen to develop high resistances to bacterial pathogens causing infections for which they were commonly prescribed. Co-trimoxazole in particular was seen to exhibit low activities of 20.5% - 66% against gram-positive bacteria including *Streptococcus pyogenes, Streptococcus pneumoniae,* non haemolytic streptococci, *Staphylococcus aureus* and *Staphylococcus epidermidis*. Ampicillin, despite showing relatively high activities of 71 - 89.7% against streptococci, exhibits very low activities of between 16.0 and 48.5% towards staphylococci and enteric gram-negative bacilli (Tables 4.2.4 & 4.2.5). Penicillin and erythromycin which are considered antibiotics of choice in treating *Streptococcus pyogenes* infections (Wessels, 2005:825-826) currently exhibit activities of 60.0% and 60.5% respectively towards the organisms (Table 4.2.4). The misuse or over-use of these antibiotics is seen as fundamentally contributing to development of resistance of these organisms towards the antibiotics.

Summary: Research Phase I

Antibiotic prescriptions emanating from inpatient and outpatient departments of five selected public health institutions in Lesotho have been analysed and reported for their appropriateness in this Phase of the study. The impact of appropriateness of antibiotic prescribing on treatment outcome indicators as well as costs of antibiotic treatments have also been determined and reported. In addition, estimations of the effectiveness of patterns of antibiotic prescribing in treating diagnosed infections based on activities of prescribed antibiotics against bacterial isolates commonly associated with given infections as determined in Phase II of the study, have also been made and presented. In Phase II of the study, culture sensitivity test results data collected over a six and a half year period from January 2000 to June 2006 had been analysed to determine pathogen associations with diagnosed infections and antibiotic sensitivity patterns of bacterial isolates. The findings of this phase of the study are evaluated and discussed in the sections that follow.

4. 2 EMPIRICAL RESEARCH PHASE II: BACTERIAL PATHOGENS - ASSOCIATIONS WITH INFECTIONS AND ANTIBIOTIC SENSITIVITY PATTERNS

The section presents results of Phase II of the study which sought to establish antibiotic sensitivity patterns of bacterial pathogens commonly isolated at study sites, bacterial pathogen associations with infections commonly diagnosed and treated at study site hospitals and procedures of selecting antibiotics appropriately for the empiric treatment of infections.

Bacterial isolates reported in the presentations are named by their species or taxonomic names as provided by laboratories. In the special case of streptococci isolates, laboratories most of the time identified them by their characteristic group names that define them as α-, β-, or non-haemolytic streptococci and not by the taxonomic or biological names of actual isolates. In results presentations both laboratory reported group names of these pathogens and the biological names of principal members of the groups were listed for reasons of identifying the principal group members with infections they are associated. Such principal group members as indicated against laboratory indicated group names are *Streptococcus pneumoniae* for α- haemolytic streptococci and *Streptococcus pyogenes* for β-haemolytic streptococci (Table 2.1). Non-haemolytic streptococci refer to either isolates of enterococci (*Enterococcus faecium* or *Enterococcus faecalis for example*) or other streptococci that do not haemolyse blood cells. Where found necessary these are listed together with the laboratory indicated group name, non-haemolytic streptococci (Table 2.1).

4.2.1 Bacterial pathogens commonly isolated at study sites

This step of the study investigated frequencies of isolations of bacterial isolates from respective study sites. Total number of pathogens isolated within the study period and their percentage distribution within the respective study sites determined. Various pathogens isolated from study site laboratories. Frequencies of isolations of bacterial pathogens from specimen types sent to different study site microbiology laboratories would expectedly be different depending on the capabilities of study site hospital laboratories to grow and isolate pathogens from given specimens as well as the epidemiological patterns of infections within respective HSAs served by these hospitals. this and discussed its relevance as presented below under results evaluation and discussion.

4.2.1.1 Results

- **Percentage frequency isolation of pathogen from all specimens at all sites**

Table 4.2.1 shows frequencies of isolation of all pathogenic bacteria isolated at all five study sites from January 2000 to June 2006. By records of percentage frequencies of isolations of such bacteria as the table and also Figures 4.2.1, 4.2.2, 4.2.3, and 4.2.4 depict, the following are reported as patterns of bacteria pathogen that are commonly isolated at all study sites considered together:

- A total of 5007 isolations of bacteria composed of various species and types of pathogenic bacteria was investigated from January 2000 to June 2006 for all five study sites.
- Of the total number of isolations carried out at all sites, a majority 71.0%% were done at the Queen II Hospital. Maluti, Motebang, Scott and Berea hospitals respectively contributed 14.0%, 6.0%, 6.0%, and 3% to the remaining 29% of isolations.

Gram-positive isolates

- Gram-positive bacteria isolated gram-positive cocci *Staphylococcus aureus* (26.5%), non-haemolytic streptococci [enterococci and non enterococcal streptococci] (3.1%) β-Haemolytic streptococci (*Streptococci pyogenes*) (2.3%), α-Haemolytic streptococci (*Streptococcus pneumoniae*) (2.2%), *and Staphylococcus epidermidis* (1.0%) *(also known as Staphylococcus albus* (Cheesbrough, 2000:62) *Staphylococcus saprophyticus* (0.08%), was reportedly isolated only at the Queen II Hospital.

- *Corynebacterium* spp a gram-positive bacilli was also isolated but at an insignificant percentage frequency of 0.08%.

Gram-negative isolates

- Gram-negative bacilli isolated were *Escherichia coli* (35.4%), *Proteus* spp (11.0%), *Klebsiella* spp (10.1%) and *Pseudomonas aeruginosa* (6.6%). Other species of the group isolated at insignificant rates included *Acinetobacter* spp

(0.26%) and *Haemophilus influenzae (0.26%, Haemophillus parainfluenzae 0.02%*, *Salmonella* spp (0.08%), *Shigella* spp (0.06%) (0.08).

- *Neisseria gonorrhoea,* a gram-negative cocci was isolated at an insignificant percentage frequency of 0.42%.

Anaerobic bacteria

- Anaerobic bacteria comprising *Peptococcus* and *Bacteroides* were isolated at rather insignificant percentage frequencies of 0.12% and 0.06% respectively.

- **Bacteria pathogen isolation by study sites**

Figures 4.2.3, 4.2.4 and 4.2.5 show percentage frequencies of bacteria pathogen isolations at individual study sites with Figure 4.2.3 showing such frequencies of isolation for gram-positive cocci pathogens and Figures 4.2.4 and 4.2.5 those of gram-negative bacilli and anaerobic bacteria respectively. Patterns of individual frequencies of isolation depict the following:

Gram-positive bacteria

- *Staphylococcus aureus* was isolated at appreciably high rates at all study site hospitals. Of the total number of the pathogens isolated 56.9% came from the Queen II hospital, 18.8% from Maluti, 12.1% from Scott, 6.3% from Motebang and 5.9% from Berea hospitals.
- *Staphylococcus epidermidis* was mainly isolated from the Queen II and Maluti Hospitals from which 58.4% and 34.0% of the total isolates of the pathogen were obtained. Comparatively, very low relative frequencies of isolation of 4.0% of the organism were each obtained from the Berea and Motebang hospitals. No isolates of the pathogen were obtained at the Scott hospital

Table 4.2.1 Frequencies of bacteria pathogen isolation according to study sites from Jan 2000 to June 2006

Bacterial Isolates	Frequencies of pathogen isolation at study sites											
	Berea Hospital		Maluti Hospital		Motebang Hospital		Queen II Hospital		Scott Hospital		Total	
	n	n%	N	n%	n	n%	n	n%	n	n%	n	n%
β-Haem streptococci (*S. pyogenes, S. agalactiae*)	2	1.24	23	3.3	9	2.81	76	2.18	5	1.81	115	2.3
α-Haem streptococci (*S. pneumoniae*, Viridans strept)	0	0	38	5.45	11	3.44	61	1.75	1	0.36	111	2.2
Non-haemolytic streptococci (Enterococci and non-enterococcal streptococci)	1	0.62	80	11.48	4	1.25	70	2.1	0	0	155	3.1
Neisseria spp	1	0.62	2	0.29	1	0.31	16	0.46	0	0	20	0.40
Peptococcus spp	1	0.62	1	0.14	0	0	4	0.11	0	0	6	0.05
Staphylococcus aureus	78	48.1	250	35.87	84	26.3	756	21.7	161	57.3	1329	26.5
Staphylococcus epidermidis/albus	3	0.8	26	3.7	3	0.9	45	1.3	0	0	51	1.0
Staphylococcus saprophyticus	0	0	0	0	0	0	4	0.11	0	0	4	0.08
Acinetobacter spp	0	0	0	0	0	0	13	0.37	0	0	13	0.26
Bacteroides spp	0	0	0	0	0	0	3	0.09	0	0	3	0.06
Escherichia coli	18	11.1	131	18.8	110	34.4	1460	41.9	52	18.5	1771	35.4
Haemophilus influenzae	0	0	3	0.4	0	0	7	0.2	3	1.07	13	0.26
Haemophilus parainfluenzae	0	0	0	0	0	0	1	0.03	0	0	1	0.02
Klebsiella spp	22	13.6	46	6.6	19	5.94	392	13	28	9.96	507	10.1
Pseudomonas aeruginosa	8	4.9	37	5.3	31	9.69	246	7.1	6	2.14	328	6.55
Proteus spp	28	17.3	56	8	48	15	399	11.5	21	7.47	552	11.02
Salmonella spp	0	0	0	0	0	0	3	0.09	1	0.36	4	0.08
Shigellae spp	0	0	0	0	0	0	2	0.06	1	0.36	3	0.06
Corynebacterium spp	0	0	4	0.6	0	0	0	0	0	0	4	0.08
Total isolations	162	100	697	100	320	100	3483	100	274	100	5006	100

Notations: n% value determinations based on row totals

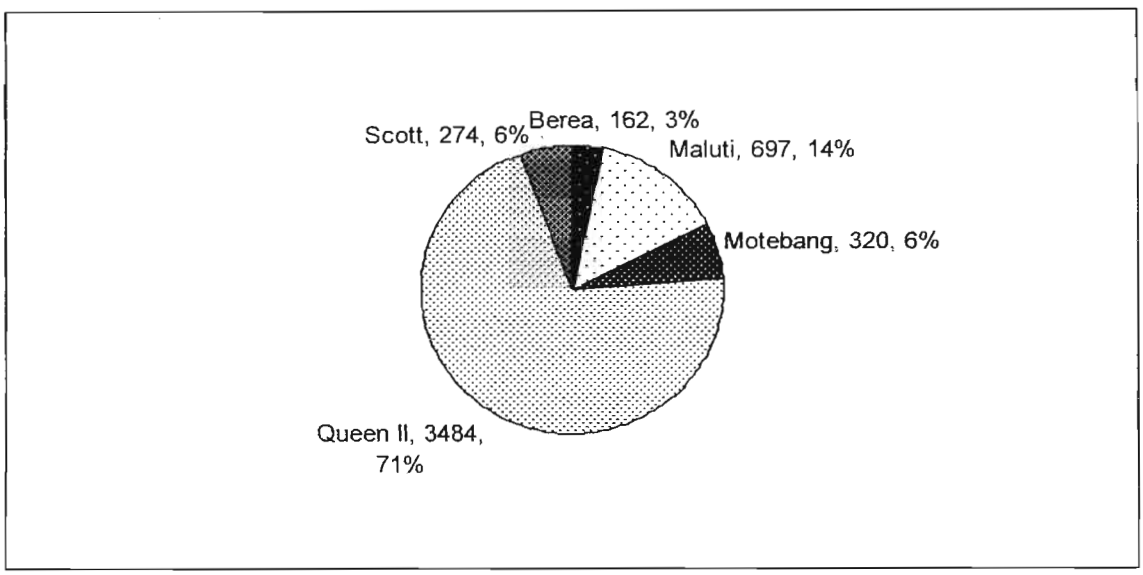

Figure 4.2.1 Frequencies of pathogen isolation at study sites from Jan 2000 to June 2006

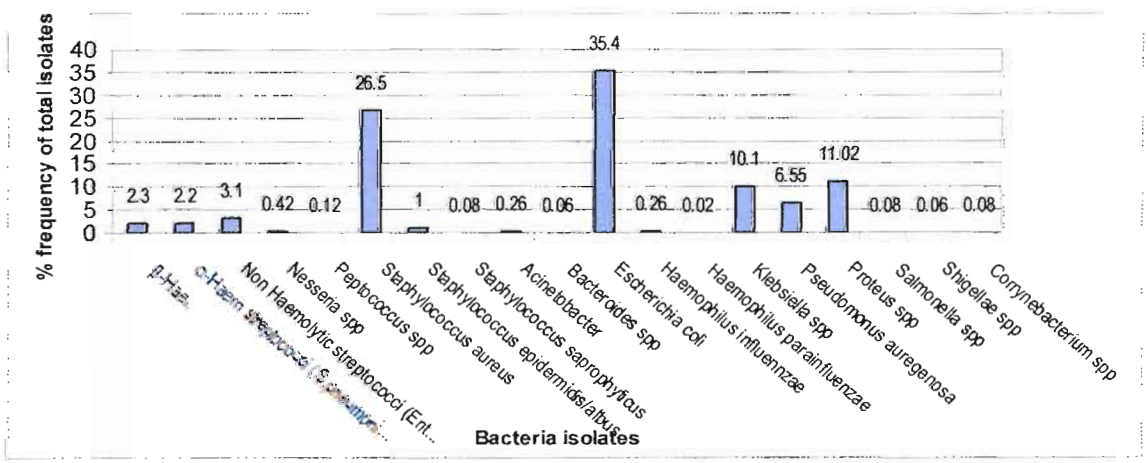

Figure 4.2.2 Frequency distribution of bacterial isolates from all study sites from Jan 2000 to June 2006

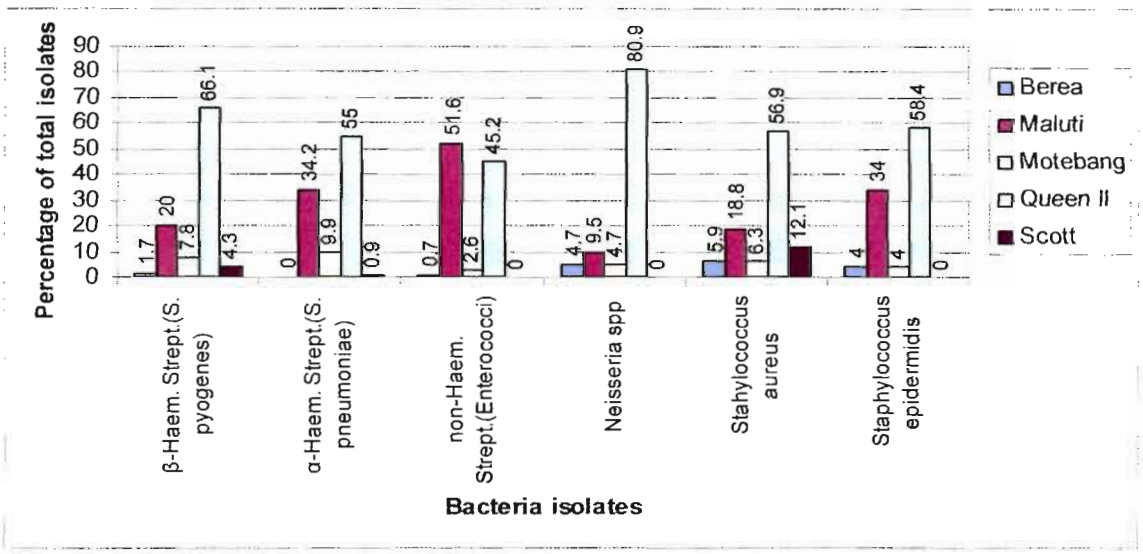

Figure 4.2.3 Percentage frequency distributions of gram-positive cocci isolates at study sites (Jan 2000 to June 2006)

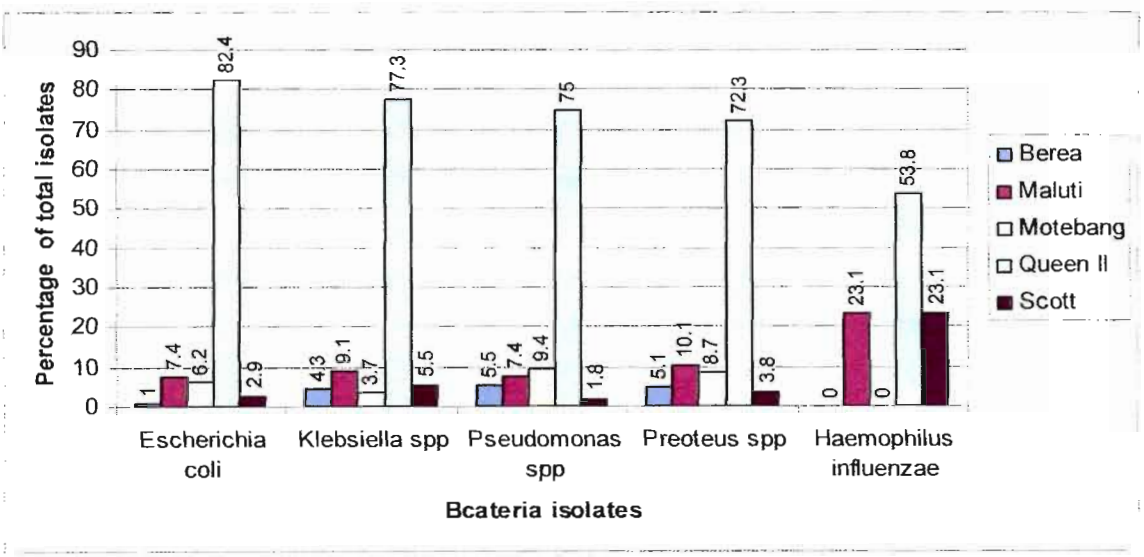

Figure 4.2.4 Percentage frequency distributions of gram-negative bacilli isolates at study sites (Jan 2000 to June 2006)

- Of the total number of β-haemolytic streptococci (*Streptococcus pyogenes*) isolates, 66.1%, 20.0%, 7.8%, 4.3% and 1.7% were from the Queen II, Maluti, Motebang, Scott and Berea hospitals.
- Of the total number of isolates of α-haemolytic streptococci (*Streptococcus pneumoniae*) isolated, 55.0%, 34.2%, 9.9% and 0.9% were isolated respectively at the Queen II, Maluti, Motebang, Scott hospital. No isolates of the pathogens was isolated at the Berea hospital.
- Non-haemolytic streptococci (*Enterococcus faecalis* or *Enterococcus faecium* and non-enterococcal streptococci) were isolated at percentage frequencies of 51.6% at the Maluti hospital 45.2% at Queen II, 2.6% at the Motebang and 0.6% at the Berea hospital. No non-haemolytic streptococci isolates were reported isolated at the Scott hospital.

Gram-negative bacteria

- All four gram-negative bacilli showing dominance in isolation among the morphological grouping, namely, *E. coli, Klebsiella* spp, *Pseudomonas aeruginosa* and *Proteus* spp had high relative frequencies of isolation at the Queen II hospital where they respectively isolated at percentage frequencies of 82.4%, 77.3%, 75.0%, and 72.3%. The pathogens showed rather far lower rates of isolation at other study site hospitals in comparison with the Queen II hospital.
- Of the total number of isolates of *E. coli*, 7.4% were isolated at the Maluti hospital, 6.2% at Motebang hospital, 2.9% at the Scott hospital and 1.0% at the Berea Hospital.
- Of the total number of isolates of *Klebsiella* spp 9.1%, 5.5%, 3.7%, 4.3%, of the pathogen were respectively isolated at the Maluti, Scott Berea and Motebang hospitals.
- Of the total number of isolates of *Pseudomonas aeruginosa* 9.4% were isolated at the Motebang hospitals, 7.4% at Maluti hospital, 5.5% at Berea hospital and 1.8% at the Scott hospital.
- *Proteus* spp similarly were isolated at rates of 10.1% at Maluti hospital, 8.7% at Motebang hospital, 5.1% at Berea hospital, and 3.8% at the Scott hospital

- Of the total number of isolates of *Haemophilus influenzae* 53.0% and 23.1% each, were isolated respectively only at the Queen II, Maluti and Scott hospitals.
- Like the gram-negative bacilli, *Neisseria spp*, the only gram-negative cocci that had been isolated, was isolated mainly from the Queen II hospital. Of the total number of isolates of the pathogen 80.9% were isolated from this hospital with 9.5% being isolated at the Maluti hospital and 4.7% each being isolated at the Berea and Motebang hospitals.

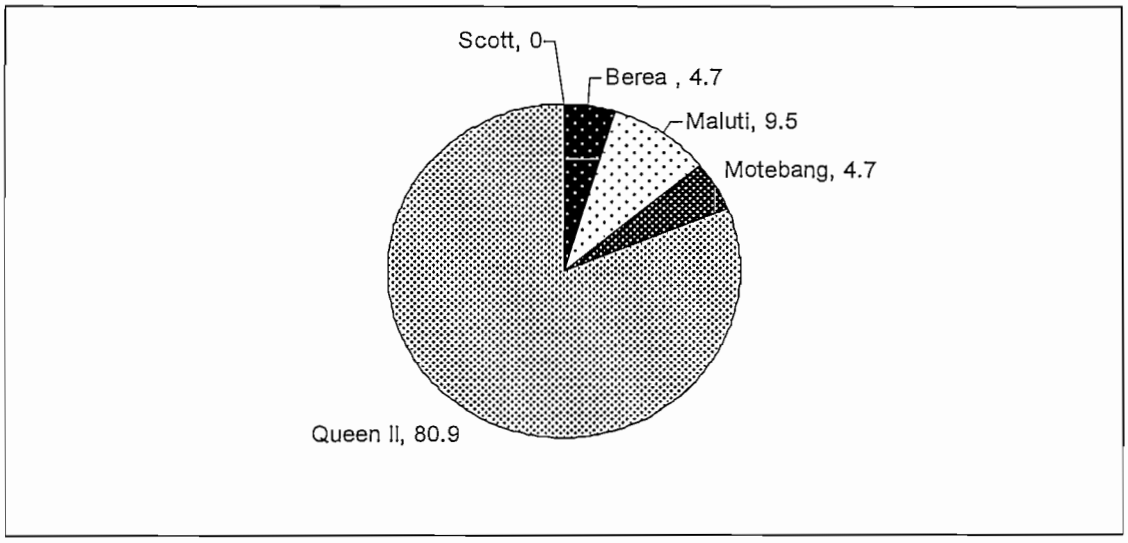

Figure: 4.2.5 Frequencies of Neisseria spp (Gram-negative cocci) isolation at study sites from Jan 2000 to June 2006.

4.2.1.2 Results Evaluation and Discussion

- **The extent of bacterial pathogen isolation at study sites**

One objective of this study was to determine and provide a list of bacterial pathogens associated with commonly diagnosed infectious diseases in Lesotho to enable their adequate antibiotic coverage in the empiric treatment of infections. The validity of such a list as had been provided from results of culture sensitivity test (CST) results data analysis, depends much on the extent to which bacterial pathogens were isolated from study site microbiology laboratories. This in itself depends on the regularity with which specimens were sent to laboratories for CST analysis and also the functional and technical capabilities of study site laboratories in the isolation and identification of bacterial pathogens implicated in infections for which specimens were obtained.

By inference from results of study Phase I which reports results of prescription assessment for their appropriateness, prescribers at study site hospitals can be said to use microbiology laboratory facilities at their disposal very scantily to aid their diagnosis and treatment of infections. Results of this phase of the study showed only 1.3% of inpatient antibiotic prescriptions assessed and none of outpatient such prescriptions to be written based on culture sensitivity test results. This inference was lent much credence by results of study Phase III which also reported general reluctance on the part of prescribers to use laboratory facilities at their disposal in the diagnosis and appropriate selection of antibiotics in the treatment of infections (Sections 4.3.4 & 4.3.7). Generally therefore, specimens meant for analysis for their microbial composition can be said to be sent to study site laboratories with a regularity that lacked the potential to generate a data base which, when analysed, would provide results that reflect the true spectrum of bacterial pathogens associated with diagnosed infections.

Functional and technical capabilities of microbiology laboratories as required in the efficient isolation and reporting of bacterial pathogens associated with specimens were found lacking as essential components in the operational activities of laboratories. These were largely considered as compromising frequencies of bacterial pathogen isolation and reporting by laboratories generally. In the course of data collection, some study site laboratories were observed to either become incapacitated in carrying out culture sensitivity tests or not to have the means technically to carry out tests on certain

specimens or isolate some species of bacteria pathogens. That this was evidenced as a shortcoming of the data collection was shown by the non-examination of sputum specimen at the Scott hospital laboratory. This, as attested to by the Chief Laboratory officer of the hospital (2006) in an interview, was due to lack of the technical means of analysing these specimens. According to records of culture sensitivity test results from which data were compiled, Berea hospital was also observed to have stopped examining certain specimens during the period for which data were collected. This most probably were for reasons that may not be different from functional or technical incapacitation as cited above. Some examples to substantiate possible compromise of data resulting from this include the lack of sufficient CST data on such pathogens as *Acinetobacter* spp, *Bacteroides* spp, *Salmonella* spp and *Staphylococcus saprophyticus* which were isolated only at the Queen II hospital microbiology laboratory; the rare isolation of *Corynebacterium* spp which also was seen only at the Maluti hospital; and the scanty frequencies of isolation of *Neisseria* and *Haemophillus* spp (Table 4.2.1).

By these assessments, it is thought that reported types of bacterial isolates and their percentage frequencies of isolation may not reflect exactly all types and rates of isolation of pathogenic bacteria abounding within Health Service Areas served by the study site hospitals and the country at large. Pertaining to bacterial pathogens' association with infections or their sensitivities to antibiotics, results of this analysis may for the above limitations be taken only as estimates of what could have been obtained if microbiology laboratories had established more complete monitoring or surveillance of bacteria as aetiological agents of various infections in the country. Research microbiology laboratories which could more appropriately assume such responsibilities, are conspicuously absent in Lesotho. This problem is not peculiar to Lesotho. It is a problem associated with most developing countries. Making a note on this, Archibald and Reller (2001:302) indicated in their review of problems of limited microbiology resources in developing countries that, due to lack of needed microbiologic resources in developing countries, causes of many infections among inpatients in Africa, Southeast Asia and the Indian subcontinent and parts of the Americas remain unknown. The authors further mentioned that to diagnose and treat infections appropriately and to fully characterise emerging infections in developing countries, enhanced clinical microbiology laboratories are a priority.

Within the limits of these reported handicaps in bacteria isolation and identification, the observed patterns of bacterial isolates as reported in the results of this study, can nevertheless be considered as providing useful information on the most common types of bacterial pathogens encountered in the country's hospitals.

- **Patterns of Bacterial pathogens' isolation at study sites**

Staphylococcus aureus with the gram-positive cocci group of pathogenic bacteria, is the most frequently isolated and hence the commonest bacterial isolate in infections in which staphylococci were identified at all study site hospitals (Figure 4.2.3).

Staphylococcus epidermidis with an isolation rate of only 1.0% at all study sites can be considered as a rarer pathogen implicated in staphylococci infections at study site hospitals. Its isolation rates of 58.4% and 34.0% at Queen II and the Maluti and hospitals, however, make them worth considering as organisms of importance in staphylococci infections when it comes to antibiotic selections in these hospitals (Table 4.2.1). The organism is less associated with infections at the Berea and Motebang and Scott hospitals but these associations must be interpreted with caution in light of limitations of this aspect of the study as indicated in paragraphs above.

Staphylococcus saprophyticus was isolated at an insignificant rate of 0.11% only at the Queen II hospital. This results indicate a less common involvement of *S. saprophyticus* in infections like urinary tract infections in young women, with which the pathogen is commonly associated. Until results of other studies indicate otherwise in its rate of isolation, the coverage of the pathogen in the empiric treatment of infections may be considered only if there is good reason to suspect the implication of the pathogen in the given infection being treated.

Streptococci organisms (β -, α- and non-haemolytic streptococci) are generally seen to be isolated at lower rates (Figure 4.2.2) at all hospitals. High percentage proportions of isolates of the organisms, 45.2% to 66.1% and 20% to 51.6% were, however, seen at the Queen II and Maluti hospitals respectively (Figure 4.3.3) as compared to the low percentage fractions of total isolates (0.0% - 9.9%) seen at other study site hospitals. This trend of isolation rate was again very highly subject to interpretations within the context of limitations of the study as indicated. Considering that these organisms are

most of the time associated with respiratory tract infections and the observation that some study site hospitals do not perform sputum analyses, this trend of isolation of streptococci as observed might truly not reflect what should be the case. With the observed high rates of isolation at the Queen II and Maluti hospitals where sputum analyses for microbial isolates are regularly done (Table 4.2.1), chances are that these organisms may equally present as aetiological agents in respiratory tract infections and may warrant their coverage in the empiric prescription of antibiotics for infections with which they are associated.

Like *Staphylococcus aureus*, *Escherichia coli* emerged within the gram-negative bacilli group of pathogenic bacteria at all study site hospitals as the most frequently isolated and hence the most common bacteria isolated in infections in which gram-negative bacilli organisms are implicated as aetiological agents (Figure 4.2.4). High rates of isolation of the organism are particularly associated with the Queen II hospital where 82% of the total number of isolates of the organism presented. Except for *Haemophilus influenzae* that had a low incidence of isolation of 0.26%, other gram-negative bacilli (*Klebsiella*, *Pseudomonas* and *Proteus* spp) were also isolated at appreciably high rates at all study site hospitals but with dominance at the Queen II hospital where 72.3% to 77.3% of total isolates of these organisms were obtained. Though isolated at lower rates at other study site hospitals, the consistency of isolation of gram-negative bacilli as shown in Figure 4.2.4 warrants the selection of antibiotics in empiric prescriptions to cover all four gram-negative bacilli organisms, *E. coli, Proteus spp, Klebsiella spp and Pseudomonas spp*, in infections in which they are associated.

The zero percentage incidence of *Haemophilus influenzae* isolation at the Berea hospital may be attributed more to irregularity of culture sensitivity test requests from prescribers than the non-presentation of clinical infections at the hospital for which the organism might be a causative agent. This is particularly true in the peculiar situation of the laboratory being seen to have stopped analysing specimens for microbial identification at certain stages of its operations during the period for which culture sensitivity test results data were collected from study sites for analysis. This was confirmed from the Laboratory Technician-in-charge of the study site laboratory, Raithule (2010) who indicated in an interview that prescribers, for what ever reason, do not just request for culture sensitivity tests at the hospital. This, according to her, led to their stoppage of

carrying out culture sensitivity tests at the hospital. Other limitations withstanding, the 0.0% incidence of *Haemophilus influenzae* isolation at the Motebang hospital may be partly due to low incidences of clinical cases of *Haemophilus* infections presenting at this study site hospital (Table 4.2.1). According to reports given by the Technician in charge of the Queen II Microbiology Laboratory, Mbo-Budiaki (2009), *Haemophilus* spp are generally difficult to grow. The pathogens, apart from the true scarcity of their isolation according to the technician's report, take 72 hours or longer to grow for proper identification and testing for antibiotic susceptibility.

Neisseria spp have a low incidence of 0.42% isolation generally. The pathogens, like many others, however, showed similar patterns of distribution in which, a high percentage fraction of total isolates of the organisms obtained from the Queen II hospital (80.9%) was complemented by an almost even distribution of the remaining fraction of the isolates among other study site hospitals. This is in exception of the Scott hospital where no isolates of the pathogens were isolated during the period during which data was collected. Significant of note is the finding that all other bacterial pathogens with low incidences of isolation (less than 0.1%) were isolated at the Queen II hospital. These include the anaerobic organisms, *Bacteroides* and *Peptococcus* species, as well as *Haemophilus parainfluenzae, Acinetobacter*, *Salmonella*, *Shigella* and *Corynebacterium* species. The finding by interpretation, despite an analysis of the functional capabilities of microbiology laboratories of study sites being beyond the scope of this study, established the study site hospitals microbiology laboratory as one among the five study site laboratories with the most functional capabilities for the isolation and identification of bacterial pathogens in terms of availabilities of required facilities for microbial identification and isolation including availability of trained personnel.

The Queen II hospital mainly and the Maluti hospital microbiology laboratories to some extent showed highest rates of isolation of pathogenic bacteria. This may be demonstrative of higher functional capabilities of these laboratories than other study site laboratories in isolating and identifying pathogens. Higher patient populations by observation tend to seek medical attention at the Queen II and Maluti hospitals than other study site hospitals. Most probably also prescribers at these two hospitals might have been requesting for culture sensitivity tests in more cases of infections than prescribers at other study site hospitals. These reasons may also be acceptable in

accounting for the higher rates of pathogen isolation at these two hospitals as compared with other study site hospitals. All reasons as given above may be more acceptable in explaining the observed trend of higher rates of bacteria pathogen isolation at the Queen II and the Maluti hospitals, than reasons of variations of the prevalence of infections caused by indicated bacterial isolates at the respective study site hospitals.

4.2.2 Bacterial pathogen associations with specimens

Various specimens taken from sites of infections and which include ascitic, cerebrospinal and pleural fluids, ear, eye, pus and throat swabs, as well as specimens of blood, urine, sputum and also penile and vaginal discharges are routinely sent to microbiology laboratories for the identification of their microbial composition and for the performance of culture sensitivity tests. Bacterial pathogens commonly isolated from these specimens are considered pathogens associated with infections for which specimens are taken. Results of these are presented below.

4.2.2.1 Results

Table 4.2.2 shows the percentage frequencies of bacterial isolates from specimens taken from inpatients with diagnosis of various infections. For clarity and easier descriptive analysis of Table 4.2.2, bar charts of percentage frequency distributions of bacterial isolates from individual specimens have also been drawn and shown in Figures 4.2.5 through 4.2.15 as presented below. The total numbers of bacterial pathogens isolated altogether from given specimens over the study period have been indicated as N-values against each specimen.

- **Ascitic fluid isolates (N = 17)**
  - Both gram-negative bacilli and gram-positive cocci were isolated from ascitic fluid with gram-negative bacilli being the most often isolated of the two morphological groups of pathogens.
  - Specific pathogens isolated from the specimen included enteric gram-negative bacilli *Escherichia coli* (35%), *Klebsiella* spp (17.6%) and *Proteus* spp (5.9%). *Pseudomonas spp* an environmental gram-negative bacilli, were also isolated from the specimens at a percentage frequency of 5.9%.

- Of the gram-positive cocci group, *Staphylococcus aureus* with a percentage frequency of isolation of 17.6%, α-haemolytic streptococci (*Streptococcus pneumoniae*) and *Staphylococcus epidermidis* also with respective frequencies of isolation of 11.8% and 5.9% were the major isolates from the specimens.

- **Cerebrospinal fluid isolates (N = 78)**

  - Pathogens isolated from cerebrospinal fluid included gram-positive cocci, gram-negative bacteria (bacilli and cocci) and anaerobic organisms with gram-positive cocci dominating as the major isolates.
  - *Streptococcus pneumoniae* (α-haemolytic streptococci) with a 47.0% relative frequency of isolation was the dominant isolate from the specimens. It was followed by, from among the gram-positive cocci group of organisms, *Staphylococcus epidermidis* (18.0%), *Staphylococcus aureus* (5.1%) and non-haemolytic streptococci (Enterococci and non enterococcal streptococci) (2.6%).
  - *Neisseria* spp (gram-negative cocci) were isolated at a relative frequency of 6.1%.
  - Gram-negative bacilli isolates from the specimens included *Escherichia coli*, *Haemophilus influenzae*, *Pseudomonas*, all of which were isolated at relative frequencies of 5.1% and *Klebsiella* spp which was isolated at a frequency rate of 1.3%.
  - Bacteroides spp among the anaerobic bacteria were isolated at a percentage frequency of 3.8%.

- **Pleural fluid isolates (N = 23)**

  - Gram-positive cocci and gram-negative bacilli were all isolated from pleural fluids but with gram-positive cocci showing as the dominant pathogens. *Staphylococcus aureus* and *Streptococcus pneumoniae* (α-haemolytic streptococci) were isolated at almost respectively dominant rates of 26.1% and 21.7% respectively. Other gram-positive cocci isolated from the specimens with their indicated rates of isolation included non-haemolytic streptococci (enterococci and non enterococcal streptococci) (8.7%), *Streptococcus pyogenes* (β-haemolytic streptococci) (4.4%) and *Staphylococcus epidermidis*

(4.4%). Gram-negative bacilli isolated at similarly appreciable rates included *Escherichia coli* (13.0%) *Klebsiella* spp (8.7%) *Salmonella* spp (8.7%) and *Haemophilus influenzae* (4.4%)

Table 4.2.2: Percentage frequencies of bacterial isolates from specimens taken from patients with diagnosis of various infections

Bacterial isolates	Frequencies of bacterial isolates according to specimen											
	Ascitic fluid		CSF		Pleural Fluid		Ear swab		Eye swab		Pus swab	
	n.	n%	n.	n%	n.	n%	n.	n%	n.	n%	n.	n%
α-Haemolytic streptococci (*S. pneumoniae*)	2	11.8	37	47	5	21.7	5	1.6	1	14	37	1.5
β-Haemolytic streptococci (*S. pyogenes*)	0	0	0	0	1	4.4	1	0.3	1	14	82	3.3
Non-haemolytic streptococci (Enterococci)	0	0	2	2.6	2	8.7	12	3.8	1	14	75	3
Neisseria spp	0	0	5	6.4	0	0	0	0	1	14	10	0.4
Peptococcus spp	0	0	0	0	0	0	0	0	0	0	4	0.2
Staphylococcus aureus	3	17.6	4	5.1	6	26.1	128	41	1	14	938	37
Staphylococcus epidermidis	1	5.9	14	18	1	4.4	8	2.5	2	29	57	2.3
Staphylococcus saprophyticus	0	0	0	0	0	0	0	0	0	0	0	0
Acinetobacter spp	0	0	0	0	0	0	0	0	0	0	11	0.4
Bacteroides spp	0	0	3	3.8	0	0	0	0	0	0	3	0.1
Corynebacterium spp	0	0	0	0	0	0	2	0.6	0	0	1	0
Escherichia coli	6	35.3	4	5.1	3	13	20	6.3	0	0	411	16
Haemophilus influenza	0	0	4	5.1	1	4.4	5	1.6	0	0	2	0.1
Haemophilus parainfluenzae	0	0	0	0	0	0	0	0	0	0	0	0
Klebsiella spp	3	17.6	1	1.3	2	8.7	12	3.8	0	0	225	9
Pseudomonas spp	1	5.9	4	5.1	0	0	54	17	0	0	249	9.9
Proteus spp	1	5.9	0	0	0	0	69	22	0	0	394	16
Salmonella spp	0	0	0	0	2	8.7	0	0	0	0	1	0
Shigella spp	0	0	0	0	0	0	0	0	0	0	2	0.1
TOTAL	17	100	78	100	23	100	316	100	7	100	2503	100

Table 4.2.2 continued

Bacterial isolates	Frequencies of bacterial isolates according to specimens											
	Throat swab		Blood		Sputum		Urine		Penile discharge		High vaginal swab	
	n.	n%	n.	n%	n.	n%	n.	n%	n.	n%	n.	n%
α-Haemolytic streptococci (*S. pneumoniae*)	9	22.5	1	11	9	20	1	0.1	1	4.76	2	0.8
β-Haemolytic streptococci (*S. pyogenes*)	9	22.5	0	0	4	8.9	0	0	0	0	7	2.8
Non-haemolytic streptococci	12	30	1	11	4	8.9	40	2.3	0	0	7	2.8
Neisserla spp	0	0	0	0	0	0	0	0	0	0	4	1.6
Peptococcus spp	0	0	0	0	0	0	40	2.3	0	0	1	0.4
Staphylococcus aureus	7	17.5	2	22	15	33	1	0.1	12	57.1	157	62
Staphylococcus epidermidis	0	0	1	11	2	4.4	0	0	1	4.76	4	1.6
Staphylococcus saprophyticus	0	0	0	0	0	0	53	3.1	0	0	0	0
Acinetobacter spp	0	0	0	0	0	0	17	1	0	0	0	0
Bacteroides spp	0	0	0	0	0	0	4	0.2	0	0	0	0
Corynebacterium spp	0	0	0	0	0	0	0	0	2	9.52	0	0
Escherichia coli	0	0	0	0	0	0	1262	74	2	9.52	36	14
Haemophilus Influenza	0	0	0	0	1	2.2	0	0	0	0	0	0
Haemophilus parainfluenzae	0	0	0	0	1	2.2	0	0	0	0	0	0
Klebsiella spp	1	2.5	1	11	7	16	236	14	1	4.76	18	7.1
Pseudomonas spp	1	2.5	1	11	1	2.2	23	1.3	2	9.52	1	0.4
Proteus spp	1	2.5	2	22	1	2.2	71	4.1	0	0	12	4.7
Salmonella spp	0	0	0	0	0	0	0	0	0	0	1	0.4
Shigella spp	0	0	0	0	0	0	0	0	0	0	0	0
TOTAL	40	100	9	100	45	100	1713	100	21	100	253	100

Notation: n% value determinations are based on column totals

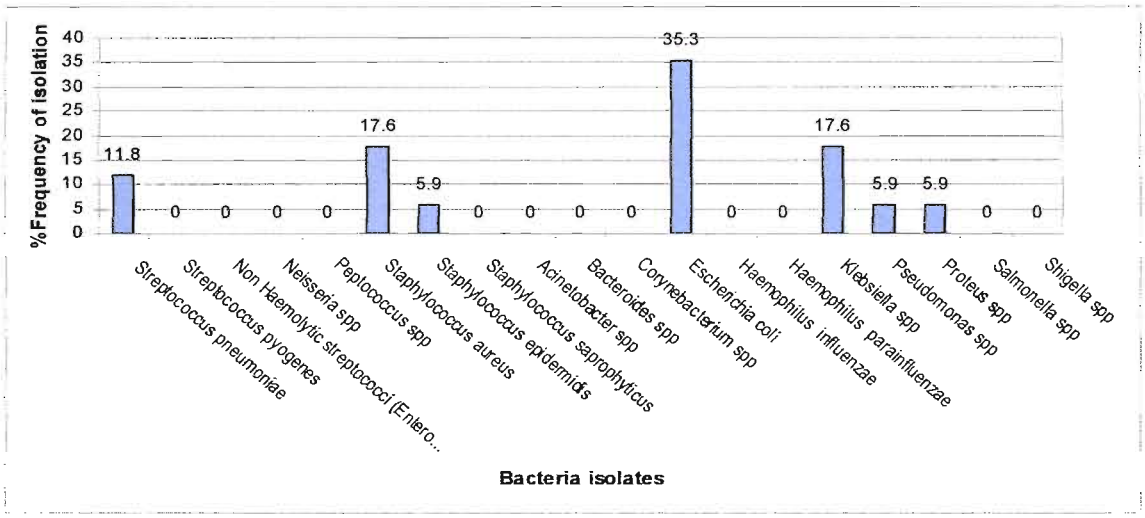

Figure 4.2.6 Percentage incidences of isolation of bacterial pathogens from **Ascitic fluid**

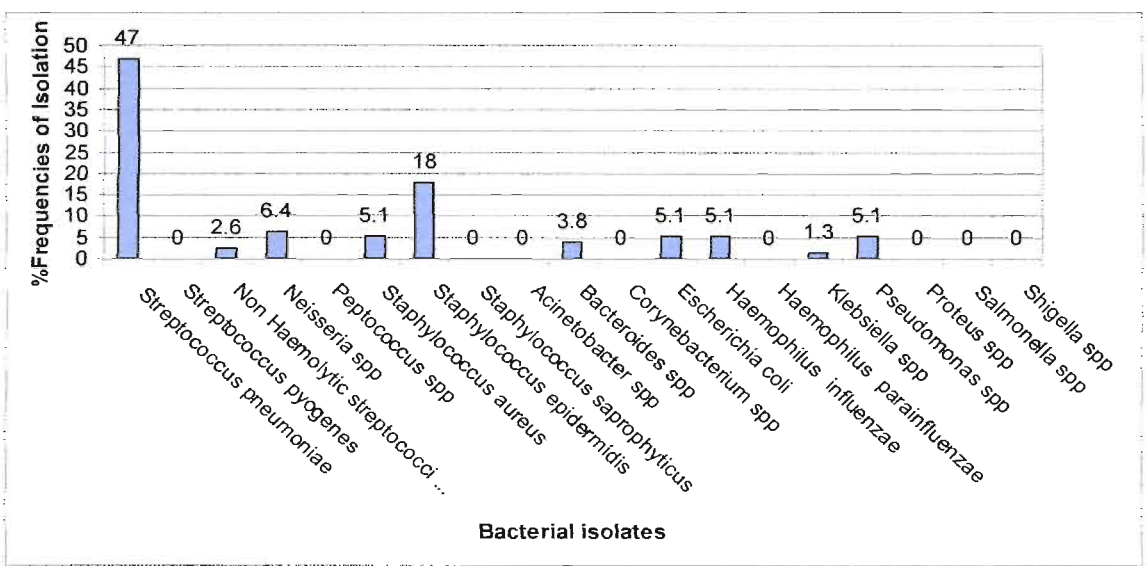

Figure 4.2.7 Percentage incidences of isolation of bacterial pathogens from **Cerebrospinal fluid**

- **Ear swab isolates (N = 316)**
  - Both gram-positive cocci and gram-negative bacilli were isolated from the specimens with a show of dominance of gram-positive cocci over gram-negative bacilli.
  - *Staphylococcus aureus*, with an isolation rate of 41% was the principal isolate from the specimens. Other gram-positive cocci isolated from the specimens with their indicated rates of isolation included *Staphylococcus epidermidis* (2.5%), *Streptococcus pneumoniae* (α-haemolytic streptococci) (1.6%), *Streptococcus pyogenes* (β-haemolytic streptococci) (0.3%) and non-haemolytic streptococci (enterococci and non-enterococci) (3.8%).
  - *Proteus* and *Pseudomonas* spp that were respectively isolated at percentage frequencies of 22% and 17% were the major gram-negative bacilli isolated from specimens of ear infections. Other gram-negative bacilli isolates were *Escherichia coli* (6.3%), *Klebsiella* spp (3.8%) and *Haemophilus influenzae* (1.6%).
  - *Corynebacterium spp with an isolation rate of 0.8% can be considered as rarely associated with ear infections.*

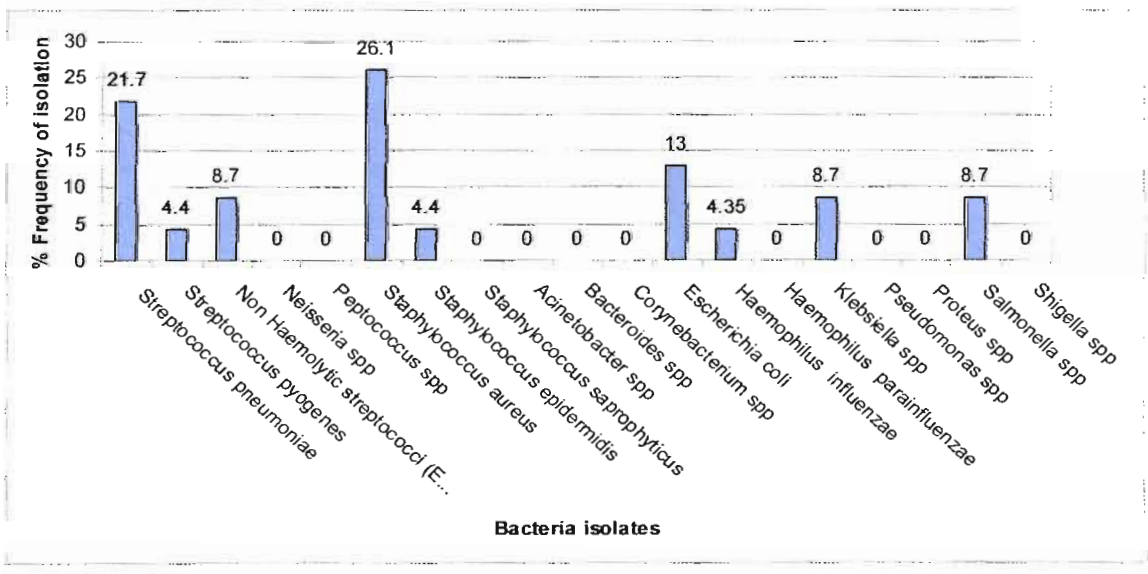

Figure 4.2.8 Percentage incidences of isolation of bacterial pathogens from **Pleural fluid**

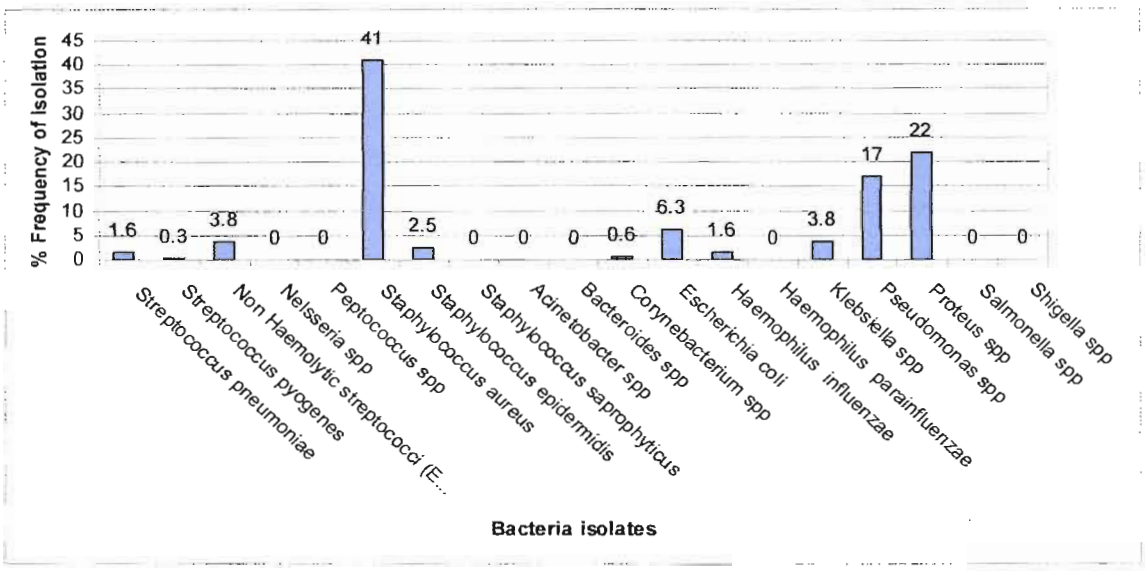

Figure 4.2.9 Percentage incidences of isolation of bacterial pathogens from **Ear swab**

- **Throat swab isolates (N = 40)**
  - Gram-positive cocci and gram-negative bacilli were both isolated from throat swab specimens but with dominance of the former morphological grouping over the latter.
  - Non-haemolytic streptococci (enterococci and non-enterococci) with a percentage frequency of isolation of 30.0% emerged as the most commonly isolated pathogen among gram-positive cocci isolates. *Streptococcus pneumoniae* (α-haemolytic streptococci), *Streptococcus pyogenes* (β-haemolytic streptococci) and *Staphylococcus aureus*, were isolated respectively and at similar percentage frequencies of 22.5%, 22.2%, and 17.5%.
  - Gram-negative bacilli isolated from the specimens included *Proteus*, *Klebsiella* and *Pseudomonas* spp. Compared to gram-positive cocci, they were isolated at much lower percentage frequencies of 2.5% each.

- **Eye swab isolates (N = 21)**

  - Gram-positive cocci, unlike observed for other specimens, were the only pathogens isolated from eye swab specimens.
  - *Staphylococcus epidermidis*, isolated at a percentage frequency of 29.0% was seen as the most commonly isolated pathogen from specimens of eye infections. Other gram-positive cocci isolated included *Staphylococcus aureus, Streptococcus pneumoniae* (α-haemolytic streptococci) and *Streptococcus pyogenes* (β-haemolytic streptococci) all of which were isolated at equal percentage frequencies of 14.0%.

- **Pus swab isolates (N = 2503)**

Cultured pus swab specimens yielded mixed microbial flora of gram-positive cocci, gram-negative bacilli, gram-negative cocci and anaerobic organisms.

  - *Staphylococcus aureus*, isolated at a percentage frequency of 37.5%, was the dominant isolate from pus swab isolates. Other gram-positive cocci, namely, *Staphylococcus epidermidis*, *Streptococcus pneumoniae* (α-haemolytic streptococci), *Streptococcus pyogenes* (β-haemolytic streptococci) and non-haemolytic streptococci (enterococci and non-enterococci) were also isolated from the specimens, but at much lower rates of 2.3%,1.5% and 30% in comparison with *Staphylococcus aureus*.
  - Among the gram-negative bacilli individual pathogens isolated from the specimens with their indicated percentage frequencies of isolation were *Escherichia coli* (16.4%), *Proteus* (15.7%), *Pseudomonas* (9.9%) and *Klebsiella* species (9.0%).
  - Rarer pathogens isolated from the specimens with their indicated percentage frequencies of isolation were *Neisseria* spp (0.4%), *Acinetobacter spp* (0.4%), *Haemophilus influenzae* (0.1%), and the anaerobic bacteria *Peptococcus* spp (0.2%) and *Bacteroides* spp (0.1%).

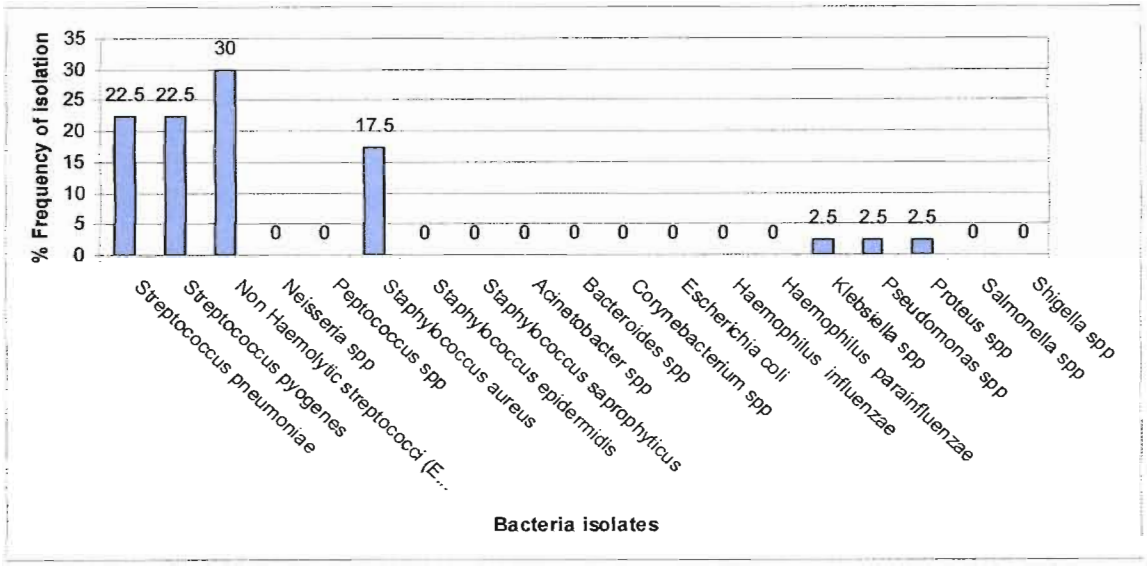

Figure 4.2.10 Percentage incidences of isolation of bacterial pathogens from **Throat swab**

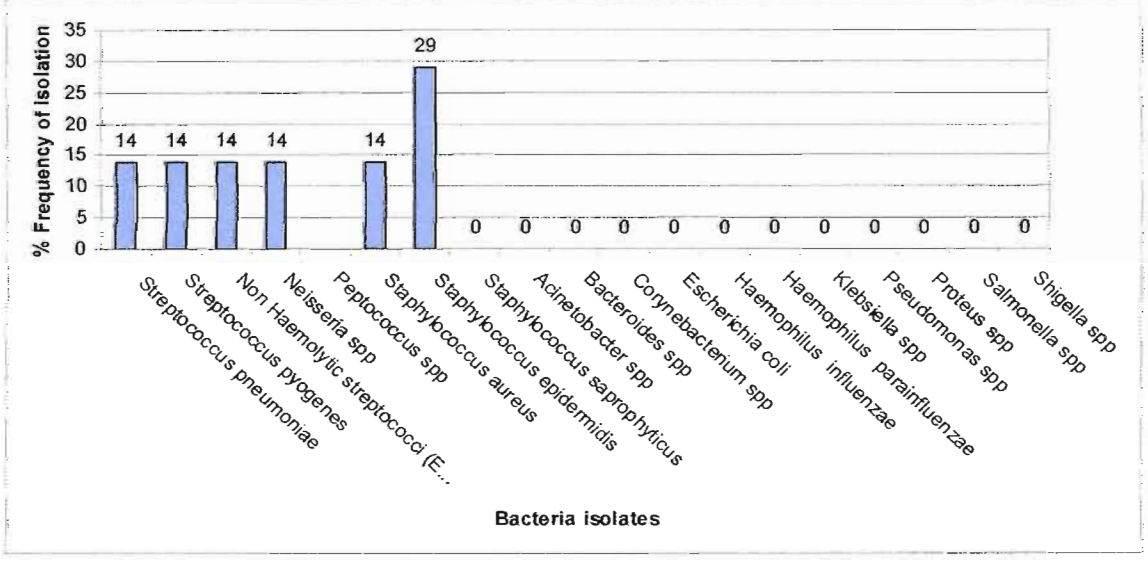

Figure 4.2.11 Percentage incidences of isolation of bacterial pathogens from **Eye swab**

- **Blood specimen isolates (N = 9)**
  - Both gram-positive cocci and gram-negative bacilli were isolated from blood specimens at similar relative frequencies of isolation.
  - Gram-positive cocci isolates from the specimens with their relative frequencies of isolation included *Staphylococcus aureus* (22%), *Staphylococcus epidermidis* (11%), *Streptococcus pneumoniae* (α-haemolytic streptococci) (11%), and non-haemolytic streptococci (enterococci and non-enterococci (11%).
  - Gram-negative bacilli isolates that were isolated from blood specimens similarly included with their relative rates of isolation *Proteus* spp (22.0%), *Pseudomonas* spp (11.0%) and *Klebsiella* spp (11.0%).

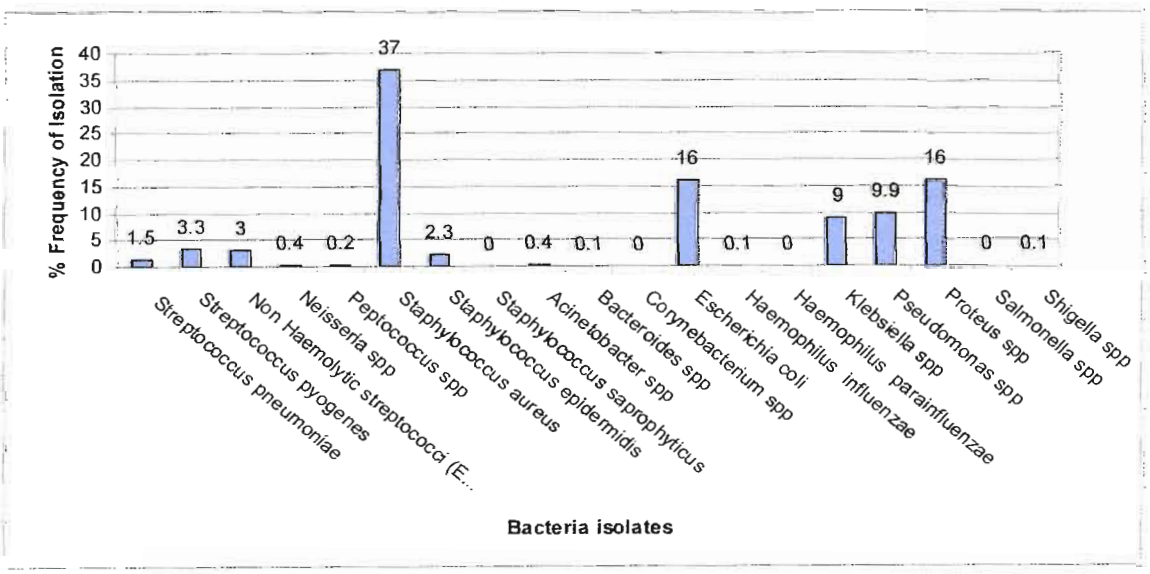

Figure 4.2.12 Percentage incidences of isolation of bacterial pathogens from **Pus swab**

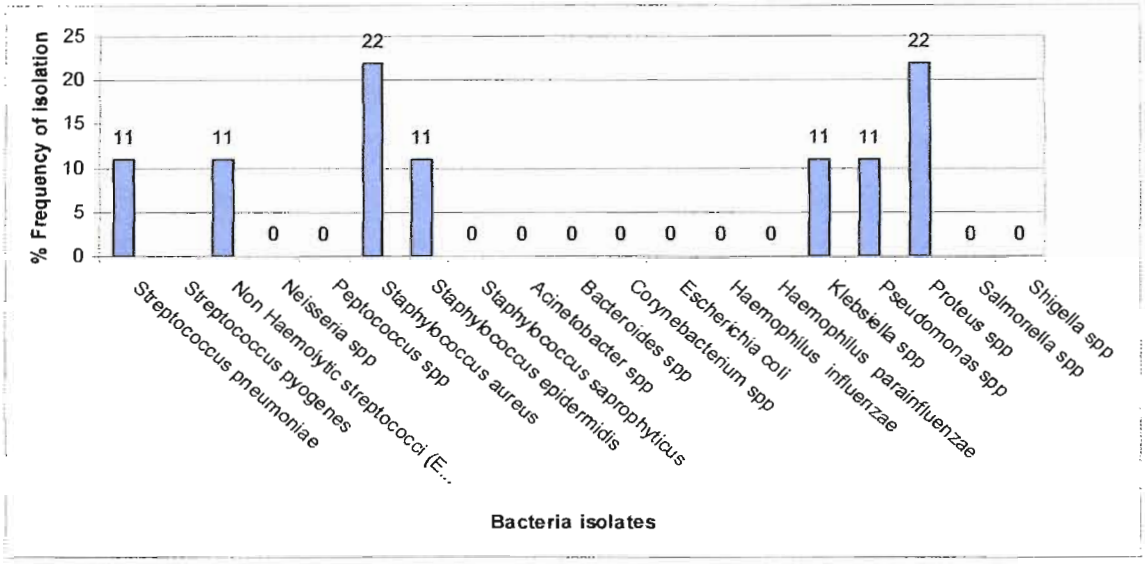

Figure 4.2.13 Percentage incidences of isolation of bacterial pathogens from **Blood**

Sputum specimen isolates (N = 45)

- Both gram-positive cocci and gram-negative bacilli have been isolated from sputum specimens but with dominance of gram-positive cocci over gram-negative bacilli as pathogens associated with the specimens.

- *Staphylococcus aureus* among gram-positive cocci was isolated at a percentage frequency of 33.3% making the pathogen the dominant isolate from sputum specimens. It is followed respectively by *Streptococcus. pneumoniae* (α-haemolytic streptococci) and *Streptococcus pyogenes* (β- haemolytic streptococci) each of which was isolated at percentage frequencies of 8.9%. Non-haemolytic streptococci (enterococci and non-enterococci) and *Staphylococcus epidermidis* were also isolated from the specimens at equal percentage frequencies of 4.4%

- Isolated at a percentage frequency of 15.6% *Klebsiella* spp were the major pathogens isolated from the sputum specimens among gram-negative bacilli. Other gram-negative bacilli isolates were isolated at much lower rates of 2.2%

each and included *Proteus* and *Pseudomonas* spp, *Haemophilus influenzae*, and *Haemophilus parainfluenzae*.

- **Urine specimen isolates (N = 1713)**
  - Percentage frequency distribution of bacterial isolates in urine specimens shows enteric gram-negative bacilli as principal isolates from urine specimens. Gram-positive cocci had also been isolated but at much lower rates in comparison with gram-negative bacilli.
  - *Escherichia coli*, with an isolation rate of 73.7% was the dominant isolate, followed by *Klebsiella* spp (13.8%), *Proteus* spp (4.1%) and *Pseudomonas* spp (1.3%).

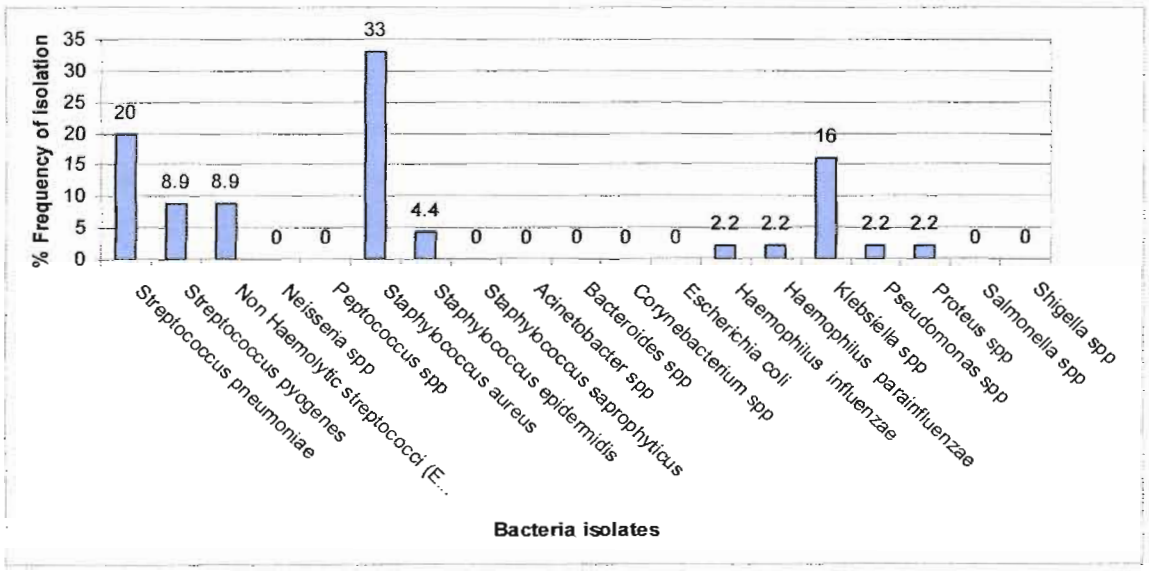

Figure 4.2.14 Percentage incidences of isolation of bacterial pathogens from **Sputum**

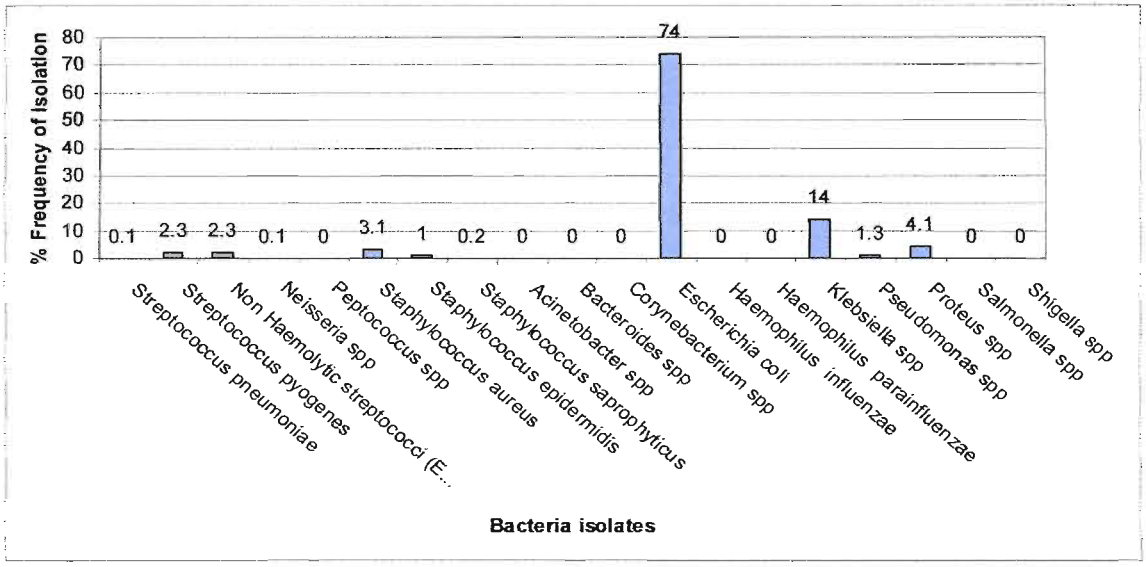

Figure 4.2.15 Percentage incidences of isolation of bacterial pathogens from **Urine**

- *Staphylococcus aureus*, *Streptococcus pyogenes* (β-haemolytic streptococci) and non-haemolytic streptococci (enterococci and non-enterococci) with respective isolation rates of 3.1%, 2.3% and 2.3% were the main gram-positive cocci organisms isolated from urine specimens. Other gram-positive cocci were isolated at rather significantly low rates and included *Streptococcus pneumoniae (*α-haemolytic streptococci) (0.1%), *Staphylococcus saprophyticus* (0.2%) and *Staphylococcus epidermidis* (1%).
  - *Neisseria* spp (gram-negative cocci) were also isolated at rather low percentage frequencies of 0.1%.

- **Penile discharge isolates (N = 21)**
  - Both gram-positive cocci and gram-negative bacilli were isolated from specimens of penile discharges but with dominance of the former morphological grouping over the latter as common isolates from the specimen.
  - *Staphylococcus aureus* among the gram-positive cocci was isolated at a percentage frequency of 57.1% and is hence considered the principal bacterial isolate from penile discharges. *Staphylococcus epidermidis* and *Streptococcus pneumoniae* (α-haemolytic streptococci) which were isolated at comparatively

much lower percentage frequencies of 4.8% were other gram-positive cocci isolates from the specimens.

- *Gram-positive bacilli Corynebacterium* spp were also isolated from the specimens at the significantly high rates of 9.5%.
- Among the gram-negative bacilli, *Escherichia coli* and *Pseudomonas* spp which were each isolated at percentage frequencies of 9.5% and also *Klebsiella* spp which were isolated at percentage frequencies of 4.8% were the major isolates.

- **High vaginal swab isolates (N = 253)**
  - A wider spectrum of pathogens, including gram-positive, gram-negative and anaerobic bacteria, than seen for penile discharges had been isolated from vaginal swab specimens.

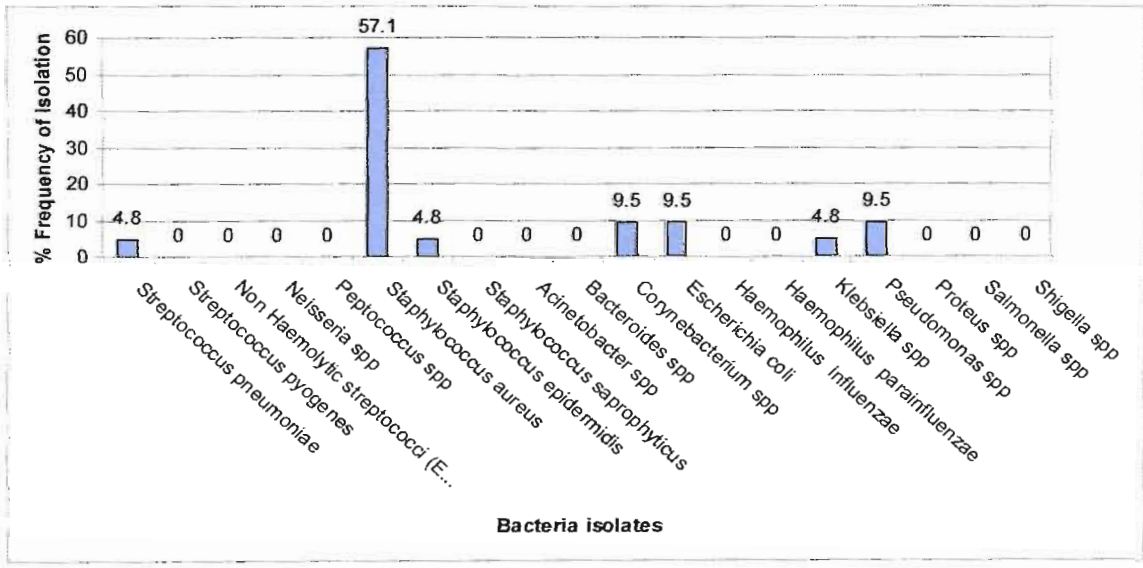

Figure 4.2.16 Percentage incidences of isolation of bacteria pathogens from **Penile discharge**

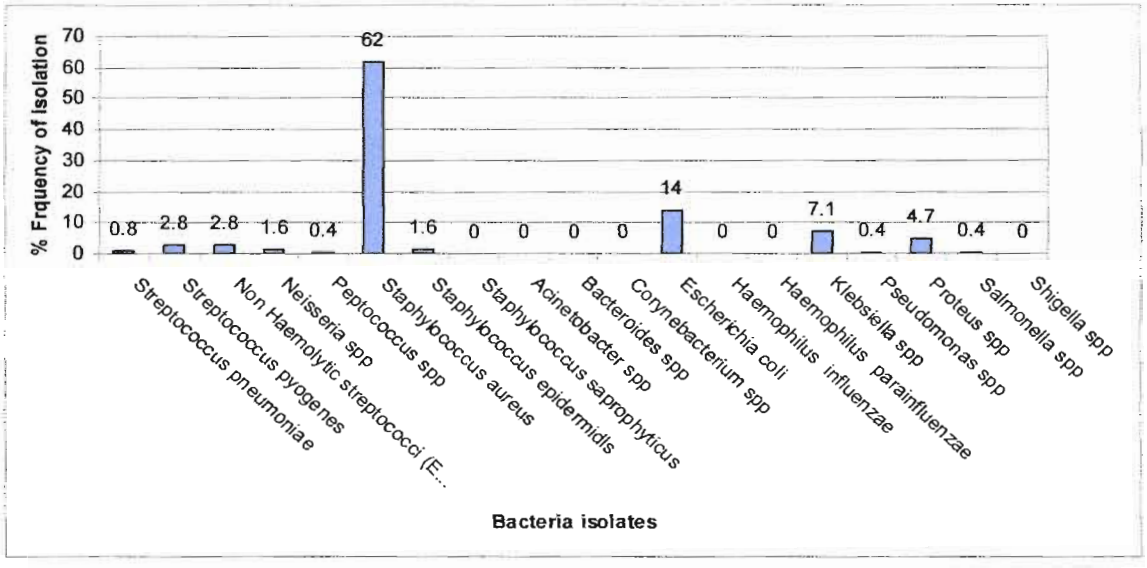

Figure 4.2.17 Percentage incidences of isolation of bacterial pathogens from **High vaginal swab**

- *Staphylococcus aureus* was isolated from the specimen at a predominant percentage frequency of 62.1%. Other gram-positive cocci isolated from the specimens included with their percentage frequencies of isolation *Staphylococcus epidermidis* (1.6%), *Streptococcus pneumoniae* (α-haemolytic streptococci) (0.8%), *Streptococcus pyogenes* (β-haemolytic streptococci) (2.8%) and non-haemolytic streptococci (enterococci and non-enterococci) (2.8%).
- Enteric gram-negative bacilli *Escherichia coli*, *Klebsiella* and *Proteus* spp were isolated among gram-negative bacteria at respective percentage frequencies of 14.2%, 7.1% and 4.7%. Other gram-negative bacteria isolated from the swab included *Pseudomonas* spp (0.4%), *Salmonella* (0.4%) and *Neisseria* spp (1.6%).
- Anaerobic organisms, *Peptococcus* spp were also isolated from the specimens though at comparatively low percentage frequencies of 0.4%.

4.2.2.2 Results Evaluation and Discussion

- **Ascitic fluid specimens: Bacterial pathogen associations with bacterial peritonitis**

Ascites in most cases may be part of a well- recognised illness like cirrhosis, congestive cardiac failure, nephrosis or disseminated carcinomatosis but the condition could also demonstrate as a complication of primary or spontaneous bacterial peritonitis or develop from portal vein thrombosis or even tuberculosis (Glickman, 2005:244). In primary bacterial peritonitis development of the ascites predates the infection. Enteric gram-negative bacteria such as *Escherichia coli* are mostly encountered but gram-positive organisms such as streptococci and enterococci or even pneumococci may also be found (Kasper, 2005:750).

The high relative frequency of isolation of *E. coli* from and the presence in ascitic fluid of other enteric gram-negative bacilli as well as *S. pneumoniae*, suggest similarities between the spectrum of organisms seen to be associated with ascitic fluid in Lesotho and literature documented bacterial spectrum associated with cases of ascites complicated with bacterial peritonitis as indicated above (Glickman, 2005:244). A strong presence of staphylococci [*Staphylococcus aureus* (17.6% frequency of isolation) and *Staphylococcus epidermidis* (5.9% frequency of isolation) (Figure 4.2.6)] in these specimens in local patients have been shown as results indicated. This is a significant difference in what both the literature and local findings purport as microbial flora associated with ascites cases complicated with bacterial peritonitis and introduces an important dimension that needs to be considered in the empiric antimicrobial treatment of the condition in local patients. The possibility of the organism occurring as contaminants should be investigated. Being common pathogens of the skin it is most probable that contaminations of specimen *Staphylococcus aureus* and *Staphylococcus epidermidis* may occur at the time they are taken. In the event of associations of the pathogens with ascites cases complicated with bacterial peritonitis, the antibiotic selection in the treatment of the infection should be made to cover staphylococci and should be based on established local bacterial pathogen sensitivity patterns.

- **Cerebrospinal fluid specimens: Bacterial pathogen associations with meningitis**

Cerebrospinal fluid (CSF) microbial flora analysis in Lesotho is done mainly in the diagnosis and treatment of meningitis and bacterial isolation from the fluid in such cases is indicative of a diagnosis of acute bacterial meningitis.

For community-acquired meningitis the literature reports *S. pneumoniae* as the most common cause in adults older than 20 years particularly in the setting of pneumococcal pneumonia as a predisposing factor or other such risk factors as co-existing sinusitis (acute or chronic), otitis media, alcoholism, diabetes, splenectomy, hypogamaglobilinaemia, complement deficiency and head trauma with basilar skull facture and CSF rhinorrhoea (Roos & Tyler, 2005:2471). Other bacteria associated with acute bacterial meningitis in the community include *Neisseria meningitidis* in both adults and children, enteric gram-negative bacilli in individuals with chronic and debilitating diseases such as diabetes, cirrhosis, or alcoholism or chronic urinary tract infections, Group B streptococcus or *S. agalactiae* in neonates and adults older than 50 years, *Listeria monocytogenes* in neonates, pregnant women, adults over 60 years, and immunocompromised individuals, *Haemophilus influenzae* type b in unvaccinated children and adults. *Staphylococcus aureus* and coagulase negative staphylococci are recognised causative agents in meningitis associated with invasive neurosurgical procedures particularly in shunting hydrocephalus and also in the Ommaya reservoirs in the administration of chemotherapeutic agents intrathetically (Roos & Tyler, 2005: 2471, 2472).

Microbial isolates from CSF as reported in the results of the study (Figure 4.2.7) has similarity with community-acquired bacterial meningitis indicated in the literature (Roos & Tyler, 2005: 2471, 2472). Special notation is, however, made of the absence of *Listeria* spp isolates and the rather strong association of coagulase negative staphylococci (*S. epidermidis*) with community acquired bacterial meningitis next to *S. pneumoniae* as the most common causative agent of the condition as well as the isolation of *Staphylococcus aureus* from CSF specimens at a significant percentage frequency of 5.1%. It is noted here that neurosurgical cases nor the use of Ommaya reservoirs for administration of intrathecal chemotherapy to which the literature attributes staphylococcal meningitis are not regular surgical procedures or methods of chemotherapeutic drug administration in Lesotho. The significant association of

staphylococci with meningitis as causative agents of the infection is hence suggestive more of being results of haematologic seeding from skin and soft tissue infections to which staphylococci are most associated than infections from sources suggested in the literature. As suggested in the case of isolations of staphylococci in ascitic fluids however, presence of staphylococci in CSF may be also be due to specimen contaminations and calls for confirmation by further investigation. Where haematologic seeding form skin and soft tissue infections are suspected or in the events further investigation confirming presence of staphylococci as associated pathogens of the infection then it may be necessary to cover the pathogens in the empiric antibiotic treatment of the infection. The isolation of anaerobic organisms (*Bacteroides* spp) in some CSF specimens also suggests consideration of antibiotics that cover these organisms in particular cases where their source as aetiological agents in bacterial meningitis is suspected in the patient.

- **Pleural effusion specimens: Bacterial pathogen associations with lower respiratory tract infections (bacterial pneumonia, lung abscess, or bronchiectasis) manifesting with parapneumonic effusions**

Depending on their aetiology, pleural effusions may be described as being transudative or exudative in type (Light, 2005:1565). By the author's definitions and explanations pleural effusions are said to be transudative when systemic factors that influence the formation and absorption of pleural fluid as seen for example in left ventricular failure, pulmonary embolism and cirrhosis are altered. Exudative pleural effusions on the other hand occur when local factors that influence the formation and absorption of pleural fluid are altered. Alterations in such factors may be caused by infections as seen for example in bacterial pneumonia, tuberculosis, fungal infections, viral infection and parasitic infections and malignancy or pulmonary embolism. Isolation of bacteria from pleural fluid is suggestive of parapneumonic effusions associated with bacterial pneumonia, lung abscess, or bronchiectasis. Both aerobic and anaerobic bacteria are involved as causative agents in bacterial pneumonia. Aerobic bacterial infections typically are responsible for acute febrile illness consisting of chest pain, sputum production and leukocytosis. Anaerobic bacteria on the other hand characteristically present with sub-acute illness with weight loss, mild anaemia, a brisk leukocytosis and a history of a factor predisposing the patient to aspiration (Light, 2005:1565 &1566)

Pathogens associated with pleural effusions as study results demonstrate (Figure 4.2.8) are all aerobic organisms with typical dominance of streptococci and staphylococci and appreciably high frequencies of isolation of enteric gram-negative bacilli and *Haemophilus influenzae* which are consistent with literature documented causative agents of bacterial parapneumonic effusions. The absence of any isolation of anaerobic organisms from pleural effusions, as results show, is indicative of the rarity of these organisms as common causative agents of bacterial pneumonia among the study population. Selected antibiotics for the empiric treatment of bacterial pneumonia should hence cover both gram-positive and gram-negative aerobic organisms and such selections should be based on local antibiotic sensitivity patterns of pathogens as determined for example at later stages of this study. A case of anaerobic organism involvement in the infection may be considered only in a clinical scenario where aspiration of gastrointestinal fluid has been established in a patient.

- **Ear swab specimens: Bacterial pathogen associations with ear infections**

Ear and throat swab specimens cultured for bacterial growth typically yield bacterial pathogens associated with upper respiratory tract infections. *Staphylococcus aureus* and streptococci as organisms associated with skin and soft tissue infections are associated with infections of external ear structures as in auricular cellulitis. *P. aeruginosa* and *Staphylococcus aureus* are typically associated with infections of the perichondrium of auricular cartilage as seen in perichondritis though other gram-negative and gram-positive organisms may be involved. The organisms, *P. aeruginosa* and *Staphylococcus aureus* are also strongly associated with infections of the auditory meatus or otitis externa resulting from a combination of heat, retained moisture and desquamation and maceration of the outer canal epithelium. Bacterial infections of middle ear structures following upper respiratory tract infections as demonstrated in acute otitis media are associated typically with pathogens of the nasopharynx, namely, *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* (Rubin *et al.*, 2005:188, 189).

Ear swab isolates reported as being associated with ear infections at study sites are dominated by *Staphylococcus aureus* and other gram-positive cocci typically *Staphylococcus epidermidis,* α- and β-streptococci and enterococci as well as *Pseudomonas* spp and other gram-negative bacilli (Figure 4.2.9). Except for the reported

rare isolation of *Corynebacterium* spp from the specimens, these demonstrated spectra of ear infection associated bacteria are consistent with what is reported in the literature reviewed above as pathogens associated with otitis externa or otitis media. Ear swabs cultured were not linked with the type of ear infections they were taken for and could only be assumed to be taken for either of the two or more types of these infections. Empiric antibiotic therapy should be directed against these organisms and should include, in cases of otitis externa, a combination of penicillinase resistant penicillins e.g. dicloxacillin and antipseudomonal quinolones e.g. ciprofloxacin as suggested in the literature (Rubin *et al.*, 2005:188) but in accordance with local antibiotic sensitivity patterns.

The equally high probability of viral aetiology in otitis media makes the use of antibiotics in treating the condition a point of debate because of the difficulty in predicting which patients will benefit from antibiotic therapy. Antibiotic therapy where considered is generally empirical because of the consistency in the documentation of similar pathogen profiles as aetiologic agents of the infection by most studies. Outcomes of studies continue to find amoxicillin as successful as any other agent in treating the infection according to Rubin *et al.* (2005:189). The antibiotic in the notice of these authors still remains a drug of choice in treating otitis media despite the increasing resistance of *S. pneumoniae* isolates to penicillin and amoxicillin and about one-third of *Haemophilus influenzae* isolates and almost all *Moraxella catarrhalis* isolates being resistant to it. Switch of regimen is, however, recommended if there is no clinical improvement by the third day of therapy as that would strongly suggest the possibility of the presence of β-lactamase producing resistant strains of *Haemophilus influenzae* and *Moraxella catarrhalis* or penicillin resistant strains of *S. pneumoniae* (Rubin *et al.*, 2005:189).

- **Throat swab specimens: Bacterial pathogen associations with throat infections**

Bacterial isolates obtained from throat swab specimens suggest a strong association of bacterial pharyngitis in the study population with all gram-positive cocci particularly, enterococci (non-haemolytic streptococci) where such association is strongest in terms of the organism's relative frequency of isolation (Figure 4.2.10). Almost equal associations of the infection with *S. pneumoniae* (α-haemolytic streptococci), *S. pyogenes* (β-haemolytic streptococci) and *Staphylococcus aureus* were observed and so

also were to a lesser degree associations with gram-negative bacilli *Proteus*, *Klebsiella* and *Pseudomonas* spp. These reported bacterial isolates from throat swab specimens is rather not consistent with literature findings that associate bacterial pharyngitis mainly with *S. pyogenes* and streptococci groups C and G and rarely with *Neisseria gonorrhoea*, *Corynebacterium diphtheriae*, *Corynebacterium ulcerans*, *Yersinia enterocolitica*, *Treponema pallidium* (in secondary syphilis) and anaerobic bacteria (Rubin *et al.*, 2005:189). This finding makes it imperative to tailor antibiotic prescription in the empiric treatment of diagnosed cases of bacterial pharyngitis in accordance with the established local spectra of pathogens seen to be responsible for the infection and the local antibiotic sensitivity patterns of these organisms as established at later stages of this study. The dominance of enterococci *(E. faecium or E faecalis*) in throat infections and even of *Pseudomonas* spp as associated pathogens of the infection prompt consideration of these organisms which are known to cause opportunistic infections mainly in immune compromised patients as emerging pathogens in the population need to be taken into consideration when these infections are treated. With prevalence rate of 24.0% (Ministry of Health & Social Welfare, 2004: 233) of HIV infection among the Basotho population, speculations are that these pathogens are emerging as important aetiological agents in infections in which they hitherto had not been commonly associated.

- **Eye swab specimens: Bacterial pathogen associations with eye infections**

Staphylococci heavily colonises the eye lids and is highly associated with the development of blepharitis or eye lid inflammation which characteristically demonstrates as purulent inflammation of sebaceous glands of the eye lids (meibomian or zeisian glands) as described for either external or internal hordeolum or stye (Horton, 2005: 165). Bacterial conjunctivitis with its characteristic mucopurulent exudate is also known to be associated with *Haemophilus influenzae* biogroup aegyptius a gram-negative organism (Murphy, 2005:866). *Clamydia trachomatis* a major cause of sexually transmitted perinatal infection is also associated with, endemic chronic conjunctivitis or inclusion conjunctivitis, in adults exposed to genital secretions (Stamm, 2005:1016). Ocular gonorrhoea with its characteristic swollen eye lid or conjunctiva and profuse purulent discharge also do manifest in patients and is associated with *Neisseria gonorrhoea* autoinfection from a genital site (Ram & Rice, 2005: 858). *P. aeruginosa* is

also an associated organism with bacterial keratitis or corneal endophthalmitis in the human eye.

Cultured pathogens from eye swab specimens typically yielded gram-positive cocci with dominance of *Staphylococcus epidermidis* and equal but lesser associations with *Staphylococcus aureus,* and streptococci [*S. pneumoniae* (α-haemolytic streptococci), *S. pyogenes* (β-haemolytic streptococci) and enterococci (non-haemolytic streptococci)] (Figure 4.2.11). These isolates are consistent with literature indicated pathogens causing blepharitis. Their non-consistency with other forms of pathogens associated with eye infections as the reviewed literature indicates, is suggestive most probably of the absence or at least the negligible occurrence of these forms of eye infections in the study population. Until other studies indicate otherwise, however, empiric antibiotic prescriptions for eye infections should be directed against gram-positive cocci but with a follow-up mechanism of patient review in place for monitoring the treated eye infection for the effectiveness of prescribed antibiotics in the event of any of the rare pathogens indicated in literature being the cause of the infection.

- **Pus specimens: Bacterial pathogen associations with wound infections**

Wounds create portals of entry through the skin and become a site of colonisation and infection for most pathogens, both aerobic and anaerobic. They provide a favourable environment for bacterial growth and hence are associated with many pathogens. The literature reports, as indicated below, a wide range of bacterial pathogens that are commonly associated with wound infections. In post-surgical wound infections *Staphylococcus aureus*, coagulase negative staphylococci, streptococci (group A streptococci), *Clostridium* spp, enteric or non-enteric gram-negative bacilli (*Escherichia coli*, *Klebsiella* spp, *Proteus* spp, *Pseudomonas aeruginosa* and anaerobic bacteria (*Bacteroides* spp, *Peptococcus* spp, *Peptostreptococcus* spp) are all commonly isolated pathogens (Weinstein, 2005:778). Staphylococci and streptococci (*Streptococcus pyogenes*) cause many of the infections involving skin, subcutaneous tissues and muscles and as such are common isolates from community-acquired wounds (Wessels, 2005:826). *P. aeruginosa* also similarly causes skin and soft tissue infections and, like the gram-positive cocci, are associated with wounds developed in the community. It has become an increasingly important pathogen in the development of skin infections in patients with AIDS and it is particularly noted to complicate third degree burns (Ohl and

Pollack, 2005:892). *Aeromonas spp* causes sepsis in infants and immunocompromised hosts and *Aeromonas* wound infections can occur in healthy adults who sustained minor trauma with environmental contamination or after severe trauma and crush injuries (Kasper *et al.*, 2005:870).

Pathogens cultured from pus swab specimens are composed of very diverse organisms as described in the literature, though with a conspicuous dominance of *Staphylococcus aureus* and an appreciably high composition of enteric gram-negative bacteria and *Pseudomonas* spp (Figure 4.2.12). While data collected did not specify sources of specimens as coming from community or hospitalised patients, it is reasonable to assume that the majority of pus swabs cultured came from inpatients since wound management procedures are undertaken more in inpatient than outpatient departments. With this assumption chances are that bacterial isolates from pus swabs would demonstrate high rates of resistance to common antibiotics available for their treatment based on findings that resistant bacterial populations flourish in areas of high antimicrobial use where they enjoy a selective advantage over susceptible populations (Archer & Polk, 2005:793). Based on this and also on the observed diverse nature of pathogens associated with wound infections, empiric antibiotic treatment of wound infections particularly from inpatient environments should be preceded always by requests of microbial identification and culture sensitivity tests before initiation of antibiotic therapy. Initial antibiotic selection according to observed spectra of bacterial isolates for pus swabs should be targeted against mixed infections of gram-positive cocci and gram-negative bacteria particularly *Staphylococcus aureus* and *Pseudomonas* spp and based on local antibiotic sensitivity patterns.

- **Blood specimens: Bacterial pathogen associations with septicaemia or bacteraemia**

Inferring from literature findings as documented below, bacteraemia or infections of blood, can be said to be associated with diverse pathogens including gram-positive and gram-negative organisms and even anaerobic bacteria. Of the major blood isolates responsible for bacteraemic episodes in patients are *Staphylococcus aureus* which characteristically causes bacteraemia complicated with endocarditis, vasculitis and metastatic seeding (Lowy, 2005:820); *Streptococcus pyogenes* which reportedly rarely causes bacteraemia without an identifiable local infection (Wessels, 2005:828); *S.*

pneumoniae which is associated with high rates of causing bacteraemia in infants and the elderly following pneumococcal pneumonia (Musher, 2005:806); *Escherichia coli* which together with *Staphylococcus aureus* are the most common clinically significant blood isolates (Russo, 2005:882). *Escherichia coli* is the gram-negative bacillus most often isolated from the blood in ambulatory settings as well as in most long-term care and hospital settings (Russo, 2005:882; Banister, 2000: 364). Its source of blood infection is most commonly from the urinary tract but can also be, in order of frequency of encounter, through abdominal, soft tissue, bone and pulmonary infections (Russo, 2005:882). Others include *Klebsiella* and *Proteus* spp (Russo, 2005:883) and *P. aeruginosa* which remain an important cause of life-threatening blood stream infection in immunocompromised patients (Ohl & Pollack, 2005:890). Among the anaerobic bacteria *B. fragilis* is the most common isolate from blood (Kasper, 2005:944).

All isolates of bacterial pathogens commonly associated with bacteraemia as reported in the literature were seen to be commonly isolated from blood specimens at study sites with appreciable relative frequencies (Figure 4.2.13). This is in exception of *Escherichia coli* which though claimed in the literature to be the most clinically significant blood isolate in addition to *Staphylococcus aureus* as well as other gram-negative bacilli most often isolated from blood in either ambulatory or hospital settings, had not been isolated even once from blood specimens. The same applies to anaerobic organisms.

Given that of all bacterial isolates from study sites *Escherichia coli* had the highest relative frequency of isolation (35.4%) and that clinical infections for which *Escherichia coli* had been isolated were all indicated as sources from which *Escherichia coli* bacteraemia can occur, it is difficult to explain the finding of non-isolation of this pathogen from blood specimens and accept its non-association with bacteraemic episodes in Lesotho as a true prevailing situation to warrant consideration in antibiotic selection and prescription in bacteraemia. An assessment of data analysed to establish rates of pathogen isolation from blood specimens (Table 4.2.1) has shown that only nine (9) bacterial isolates were obtained for the entire six-year period for which data were collected. This number of isolates is obviously too scanty for a meaningful analysis to be made for the determination of pathogens that could be deemed associated with blood specimens. The most probable and perhaps the only reason that could be given for the lack of adequate data on bacterial isolates from blood specimens is non-performance of

blood culture sensitivity tests at facilities at a rate that would generate the necessary data for analysis. This implies that antibiotic prescriptions in septicaemia are done many of the time empirically to the detriment of good patient management for bacteraemic episodes. The non-association of *Escherichia coli* with bacteraemic episodes among the study population is an important deviation from what should be considered a norm in *Escherichia coli* infection of blood as Russo (2005:882) and Banister (2000: 364) reported. It is unacceptable on the grounds of indicated limitations of the study and merits further investigation.

Empiric antibiotic prescription pending results of culture sensitivity tests is an important initial step in the management of septicaemia or bacteraemia. Choice of initial therapy is based on knowledge of likely pathogens at specific sites of local infection and generally it is important to initiate therapy that is effective against both gram-negative and gram-positive bacteria (Munford, 2005:1610). The spectrum of pathogens isolated from blood specimens and hence associated with bacteraemia in Lesotho are characteristically composed of both gram-positive and gram-negative organisms isolated at equal relative frequencies. This strongly suggests adherence to literature advocated principles in empiric antibiotic prescription in bacteraemic episodes in the country. In antibiotic selection for these treatments, however, very strict consideration needs to be given to local pathogen antibiotic sensitivity patterns provided at later stages of this phase of the study for purposes of achieving therapeutic results for which chances cannot taken.

- **Sputum specimens: Bacterial pathogen associations with lower respiratory tract infections**

Bacterial isolates from sputum are indicative of pathogens commonly implicated in lower respiratory tract infections. Such pathogens as documented in literature include *Staphylococcus aureus* which is often seen implicated in selected clinical cases including respiratory tract infections in newborns and infants and in adults as nosocomial or as post-viral community-acquired respiratory tract infections (Lowy, 2005: 818). *Streptococcus pyogenes* (β-haemolytic streptococci) which occasionally cause pneumonia and *Streptococcus pneumoniae* (α-haemolytic streptococci) which quite often causes pneumonia at extremes of age and under conditions of some underlying diseases predisposing patients to the infection (Musher, 2005: 808).

Among gram-negative bacteria *Pseudomonas aeruginosa* is associated with primary pneumonia resulting from aspiration of upper respiratory tract secretions in patients with previous antibiotic use who are exposed to hospital environment particularly intensive care units (ICUs), ventilator associated pneumonia particularly in patients with chronic lung disease, congestive cardiac failure or AIDS and respiratory tract infections in children with cystic fibrosis (Ohl & Pollack, 2005:892).
Other gram-negative organisms particularly associated with lower respiratory tract infections are *Haemophilus influenzae* often associated with community- acquired pneumonia in adults or infantile pneumonia in children (*H. influenzae type b*). (Murphy, 2005:865). Enteric gram-negative bacilli (*Escherichia coli, Klebsiella* spp and *Proteus* spp) account for only about 2 - 5% of community-acquired pneumonia. Their rates of infection, however, increase with increase in antibiotic use and severity of illness and they may become a common cause of pneumonia among residents of long-term care facilities. They are among the most frequent causes (about 60 - 70% of cases) of hospital-acquired pneumonia (Ruso, 2005:882).

Bacterial pathogens isolated from sputum have similarities in terms of types and occurrences in specimens with what have been indicated in the literature as common pathogens associated with lower respiratory tract infections (Figure 4.2.14). This is in exception of non-haemolytic streptococci (enterococci) which findings of literature search as presented above did not indicate as causative agents of respiratory tract infections but have been isolated at the same relative frequencies as other streptococci from sputum and also *Escherichia coli* which have not been isolated from any sputum specimens but which, according to Russo (2000:882) has about 60-70% chances of being the cause of hospital-acquired pneumonia.

Gram-positive cocci with an overwhelming dominance of *Staphylococcus aureus* are the most highly associated pathogens with respiratory tract infections. The equal relative frequency of isolation of non-haemolytic streptococci (enterococci) from sputum specimens as other streptococci raises concern of these organisms becoming important causative agents in respiratory tract infections in the Basotho, the principal target population from which specimens were obtained for microbial identification and antibiotic sensitivity testing. The organisms according to Wessel (2000:830) are known to produce infection in the elderly and debilitating patients or in patients in whom mucosal or

epithelial barriers have been disrupted. In terms of patients' degree of competency in wading off infections this group of patients can be considered as being less immuno-competent than otherwise healthier patients in preventing microbial colonisation and infection. A question of concern is whether the seeming emergence of enterococci as a causative agent of respiratory tract infections is a negative change in the competency of patients' immune system in combating enterococci infections and whether such a change could be linked to current rates of HIV infections among the population. Whatever the reason of this observed demonstration of high virulence of the pathogen among the population, the findings of this study have established as similarly indicated in earlier paragraphs, the emergence of enterococci as an important aetiological agent in certain infections including respiratory tract infections and such observations need to be taken into consideration in empiric antibiotic therapy of those infections among the population with which the pathogens have been associated.

Apart from *Klebsiella* spp, that demonstrated an appreciable high level of association with respiratory tract infections, gram-negative bacilli generally showed low relative frequencies of isolation and hence less of a tendency to be associated with lower respiratory tract infections in accordance with predictions from literature documented information. *Escherichia coli* in particular had not been isolated from any sputum specimens as reported above, a finding which by interpretation tends to rule out the pathogen's association with lower respiratory tract infections without parapneumonic pleural effusions. While this may be true in cases of community-acquired infections the non-isolation of the pathogen from sputum specimens of hospitalised patients in whom it is acclaimed to be responsible for up to 70% of hospital-acquired pneumonia raises concerns. As indicated for the observed non-isolation of *Escherichia coli* from blood specimens, the non-isolation of these organisms from sputum specimens of hospitalised patients is a deviation from a norm attributable most probably to non-performance of sputum culture sensitivity tests at rates that could generate sufficient data for relevant analyses to establish what truly prevails with respect to implications of *Escherichia coli* in respiratory tract infections. Further studies in which sputum specimens are to be collected specifically from both inpatients and outpatients and analysed for their microbial composition are needed to establish the true extent of *Escherichia coli* in respiratory tract infections among the study population. Based on the above results and discussions, and until such further studies are done to disprove associations of

Escherichia coli with lower respiratory tract infections among the study population, empiric antibiotic prescriptions for respiratory tract infections for which local bacterial pathogen antibiotic sensitivity patterns are taken into consideration, should cover both gram-positive cocci and gram-negative bacilli organisms, *Escherichia coli* inclusive.

Considering current high prevalence rates of HIV infection in the study population and a possible attendant increased rates of antibiotic use in the population as consequences of obvious increases in rates of bacterial infections, one would have expected rather increased rates of respiratory tract infections by *Pseudomonas* spp and paralleled increased rate of isolation of the pathogen from sputum specimens as literature information purports.

Unlike enterococci this has not been observed and pseudomonas by results of this study is yet to become an emerging pathogen in lower respiratory tract infections among the population and which has to be considered in empiric antibiotic treatments of the infection, particularly among patients contracting the infections from communal environments. Pseudomonas infections of the lower respiratory tract most commonly results from aspiration of upper respiratory tract secretions by patients according to Ohl and Pollack (2005:892) and possibilities are that most patients with lower respiratory tract infections whose sputum specimens were examined did not contract their infections by this means to facilitate pseudomonas infections. Empiric antibiotic treatment of lower respiratory tract infections in individual patients who aspirated upper respiratory tract secretions or who have other clinical conditions predisposing them to pseudomonas infections would necessarily have to take into consideration pseudomonas as target pathogens in spite of the lower association of the organisms with lower respiratory tract infections as results of the study imply.

- **Urine specimens: Bacterial pathogen associations with urinary tract infections (UTI) uncomplicated with penile and vaginal discharges**

The most common bacterial pathogens infecting the urinary tract according to Stamm (2005: 1715) and Fish (2008:64-2) are the gram-negative bacilli among which *Escherichia coli* is responsible for about 75% to 90% of cases. Other gram-negative bacilli especially *Proteus* and *Klebsiella* spp and occasionally *Enterobacter* spp account for smaller proportions and which together with *Serratia* and *Pseudomonas* spp are

particularly responsible for recurrent infections. Gram-positive cocci Stamm (2005:1715) further indicated play a lesser role in urinary tract infections. *Staphylococcus saprophyticus* accounts for 5% - 20% of acute symptomatic urinary tract infections in young women while enterococci specified as *Enterococcus faecalis* (Fish, 2008:64-2) occasionally cause acute uncomplicated cystitis in women and with *Staphylococcus aureus* more often cause infections in patients with renal stones or previous instrumentation or surgery (Stamm, 2005: 1715). Two groups of uropathogens account for urinary tract infections in women presenting with pyeuria. The first group of such patients with low leukocyte counts of 10^2 to 10^4/ml have *Escherichia coli, Staphylococcus saprophyticus, Klebsiella* or *Proteus* as infecting pathogens. In women with acute symptoms of urinary tract infection and pyeuria but with sterile urine, sexually transmitted urethritis producing agents such as *Chlamydia trachomatis*, *Neisseria gonorrhoea* and herpes simplex virus are etiologically important. More unusual bacterial pathogens with rather undefined causative roles in urinary tract infections include *Ureaplasma urealyticum* and *Mycoplasma hominis*. Both organisms are associated with prostatitis and pyelonephritis (Stamm, 2005: 1715). In hospital-acquired infections, according to Fish (2008), gram-negative bacilli notably *Escherichia coli, Pseudomonas aeruginosa, Proteus* spp, *Enterobacter* spp, *Serratia* spp and *Acinetobacter* spp are important pathogens. *Enterococcus* and *Staphylococcus aureus* among the gram-positive cocci are also important pathogens in hospital-acquired UTI with *Staphylococcus aureus* infections most often resulting from haematogenous spread or associated with urinary catheterisation (Fish, 2008: 64-2).

Major bacterial isolates obtained from urine specimens predictably correlate with literature indicated pathogens associated with urinary tract infections (Figure 4.2.15) (Stamm, 2005: 1715, Fish, 2008:64-2). Gram-negative bacilli with a 74% dominance of *Escherichia cocci* and including *Klebsiella, Proteus and Pseudomonas* spp were all reportedly isolated. Similarly gram-positive cocci inclusive of *Staphylococcus aureus*, and coagulase negative staphylococci as well as streptococci, including enterococci, were all isolated from the specimens but at much lower rates than the gram-negative organisms as indicated in the literature. Gram-negative cocci, *Neisseria gonococcus* mainly were also isolated.

A notable difference in the literature reported (Stamm, 2005: 1715, Fish, 2008:64-2) information on the spectra of pathogens associated with urinary tract infections and

results of urine specimen analysis for microbial infections reported by this research, are the reported isolations of the cocci, coagulase negative *Streptococcus epidermidis, Streptococcus pneumoniae* and *Streptococcus pyogenes* among bacterial pathogens isolated and deemed responsible for urinary tract infections in the study population. Specific bacterial virulence factors markedly influence the likelihood of a given strain of bacteria causing urinary tract infections once introduced into the bladder. As reviewed in Section 2.1.5.2.1 in respect with extraintestinal pathogenic *E. coli* (ExPEC) associated infections, possession of specific virulence factors by bacteria is very crucial in their infections of the urinary tract. An important inference from this is that organisms lacking these virulence factors or uropathogenic properties may not ordinarily infect the urinary tract except in patients with structural or functional abnormalities of the urinary tract. Uropathogenic properties of organisms, by implication are not needed for infection of the compromised urinary tract (Stamm, 2005: 1716) and the emergence of traditionally known non-uropathogens as pathogens of the urinary tract among the population as already indicated in a number of paragraphs above could have a link with acquired deficiencies in the immune system within the study population like those with HIV infections in whom defensive systems against infection generally are grossly compromised. Cassadevall and Pirofski (2000:6512), in a mini-review they made on host -pathogens interaction with focus on basic concepts of microbial commensalisms, colonisation, infection and disease, did mention, that "the catastrophe of the HIV epidemic, produced a new population of human host with impaired immune systems that were vulnerable to infections with various microbes previously thought to be non pathogenic". The extent of this statement being the reality of the situation in the Basotho population needs further investigation. As established by results of this study, and for purposes of effective empirical prescriptions of antibiotic in urinary tract infections among the study population, cognisance needs to be taken of implications of these organisms as emerging uropathogens in the population to enable their appropriate and effective treatment.

- **Penile discharge specimens: Bacterial pathogen associations with urethritis in men**

Neisseria gonorrhoeae and *Clamydia trachomatis*, which all are sexually transmitted, are the most implicated pathogens in urethritis in men (Holmes, 2005:763). The infection characteristically demonstrates urethral discharge with *C. trachomatis* contributing up to

30 to 40% of non-gonococcal form of the infection (Holmes, 2005:765). Other rather rare organisms which may be implicated in non-gonococcal urethritis (NGU) in men include *Trichomonas vaginalis*, *Mycoplasma genitalium* and possibly *Urea-plasma urealyticum* (Goad & Hess, 2008:65-11) as well as enteric gram-negative bacilli (GNB) or coliform bacteria. *C. trachomatis* and less commonly *Neisseria gonorrhoeae* are also implicated in epididymitis with associated overt urethritis. Enteric GNB (Enterobactericeae) may also be a cause of epididymitis with no urethritis in categories of men who practice rectal intercourse (Holmes, 2005:765; Goad & Hess, 2008:65-11).

Reported isolates from penile or urethral discharges as pathogens associated with urethritis, showed (Figure 4.2.16) differ markedly from literature reported associated pathogens (Holmes, 2005:765, Goad & Hess, 2008: 65-11) with the infection by having gram-positive cocci and enteric gram-negative bacilli and *Pseudomonas* spp as major isolates with a significant dominance of *Staphylococcus aureus* as the major implicating pathogen in the infection. The non-isolation of the known associated pathogens with the condition does not rule out their non-occurrence as implicating pathogens in urethritis in men but raises questions as to the functional capabilities of the laboratories to isolate and culture these organisms. This implies that antibiotic selection for treatment of urethritis in men should still cover these known causative agents.

The establishment of *Staphylococcus aureus*, other cocci and enteric gram-negative bacteria and *Pseudomonas* as major causative agents of urethritis in men (and also cervicitis - refer to discussion on bacterial pathogen associations with vaginal discharges below) in the study population completely deviates from the traditional pattern of associated pathogens with the infection as Holmes (2005:763 &765) and Goad and Hess (2008: 65-11) reported. This is a significant clinically important discovery of concern in view of notations of Cassadevall and Pirofski (2000:6512) on emerging pathogens on immunocompromised HIV patients as indicated above. This said, however, and on the basis of the possibility of the pathogens, particularly of *Staphylococcus aureus*, being contaminants of urethral discharge specimens, further investigations are suggested to establish the organisms as truly emerging pathogens in urethritis before decisions on their coverage in empiric treatment of the infections are taken.

Current treatment of the condition in both men and women in Lesotho advocates for a syndromic approach to the treatment of urethritis and vaginal discharge syndromes that principally employs an antibiotic treatment regimen (Metronidazole 400 mg twice a day, Ciprofloxacin 500 mg (per oral) or Ceftriaxone 125mg IM single dose and Doxycycline 100 mg or tetracycline 500 mg 6 hourly daily for 7 days (Ministry of Health & Social Welfare Standard treatment guidelines, 2006:66) that targets literature indicated traditional pathogens of the infection as indicated above. The regimen is seen as not taking into consideration implications of pathogens now seen to be the major causative agents of the infection. Based on these results an immediate revision of current management protocol of urethritis in men to include antibiotic treatment regimens that will effectively combat major organisms associated with the infection, with particular reference to *Staphylococcus aureus* and *Pseudomonas,* is recommended.

- **High vaginal swab specimens: Bacterial pathogen associations with vaginal discharges**

Vaginal swabs in women are taken for microbial identification in vulvovaginal infections or mucopurulent cervicitis which all demonstrated with characteristic abnormal discharges with different characteristic colours, odours or consistencies depending on type of infection. Implicating organisms include *N. gonorrhoeae* or *C. trachomatis,* which may be causes of cervical infections or mucopurulent cervicitis with increased production of yellowish vaginal fluid (Holmes, 2005:768); *Trichomonas vaginalis* characterised with the production of profuse, yellow, purulent, homogenous vaginal discharge and vulvular irritation; and *Haemophilus vaginitis, Gardnerella vaginalis, Mycoplasma hominis* (Goad & Hess,2008 65-11) and anaerobic bacteria e.g. *Prevotella* spp, *Peptostreptococcus* spp, which all may be responsible for bacterial vaginosis with its characteristic moderately increased white discharge (Holmes, 2005:767). *Staphylococcus aureus* is associated with ulcerative vaginitis and may be isolated in vaginal fluid (Holmes, 2005:768).

Microscopic characterisation of microbial composition of vaginal discharges revealed, as in the case of penile or urethral discharges in men, a dominance of *Staphylococcus aureus* as major causative agent of mucopurulent discharges in women. Though *Staphylococcus aureus* was noted in literature as an isolate of vaginal fluids associated with ulcerative vaginitis its isolation (Holmes, 2005:768) in the indicated high relative

frequency of 62% among other gram-positive cocci and gram-negative bacilli raises concern about the possible emergence of the organism becoming implicated in urethral and vaginal discharges in men and women in the study population. The possibility also remains that the pathogen could be contaminant of specimens. Further investigations are suggested to confirm this before a coverage of the pathogens in empiric treatment of these infections is considered.

Except for *Neisseria gonorrhoea* that was reportedly isolated at a low 1.6% relative frequency as well as anaerobic organisms, no other organism traditionally associated with vaginal discharges was isolated from vaginal discharges (Figure 4.2.17). While the absence of such pathogens might indicate their non-association with the infection in the population of study, a most probable lack of functional capability on the part of laboratories to isolate these pathogens from indicated specimens is a more acceptable reason for the non-isolation of the traditional pathogens associated with vaginal discharges or cervicitis. As mentioned for antibiotic therapy of penile discharges in men the coverage of these pathogens with vaginal discharges in the empiric treatment of these vaginal infections in women should be considered in antibiotic selections.

Summary

Table 4.2.3 provides a summary of associations of organisms with clinical infections as detailed in results above. Remarks on strengths of associations of bacterial pathogens with indicated infections using the descriptive terms "Very strong", "strong", "moderate" "weak" and "very weak" associations have been made based on incidences of pathogen isolation from specimens. While "strong" and "weak" associations have been used to indicate only "high" and "low" incidences of isolation of pathogens from given specimens and "moderate" for an incidence of isolation in between "high" and "low", descriptions of "very strong" and "very weak" associations have respectively been used to indicate comparatively overwhelming and very low incidences of isolation of indicated pathogens from specimens with respect to incidences of isolation of other organisms. Though used arbitrarily the terms connote descriptively expressed chances of an organism being isolated from a given specimen relative to those of other isolates and provide a basis for prescribers' decision to select given antibiotics in the empiric treatment of specified infections.

Table: 4.2.3 Summary table of associations of bacterial pathogens with specimens and clinical infections (Source: Table 4.2.2 and Results presentations of Section 4.2.2)

Specimen	Associated Clinical Infections	Commonly associated bacteria locally in Lesotho	Remarks on strengths of associations of infections with organisms by relative incidences of isolation.
Ascitic fluid	Ascites complicated with Primary or spontaneous bacterial peritonitis,	*Escherichia coli*, Klebsiella spp, *Pseudomonas* spp and *Proteus* spp (**Gram-negative bacilli**); *Staphylococcus aureus*, *Staphylococcus epidermidis* α-haemolytic streptococci (*S. pneumoniae*) (**Gram-positive cocci**).	Very strong *E. coli.* Strong associations with *Klebsiella* and *Staphylococcus aureus and Streptococcus pneumoniae .*
Cerebrospinal fluid	Meningitis	α-haemolytic streptococci (*S. pneumoniae*), non-haemolytic streptococci (Enterococci) *Staphylococcus epidermidis, Staphylococcus aureus* (**Gram-positive cocci**), *Neisseria spp* (**Gram-negative cocci**), *E.coli, Klebsiella, Pseudomonas, Haemophillus influenzae*(**Gram-negative bacilli**) Bacteroides (Anaerobic organisms)	Very strong association with *Streptococcus pneumoniae.* Strong associations with *Staphylococcus epidermidis*, Moderate associations with *Neisseria* spp and *E. coli, H. influenzae and Pseudomonas*, and weak associations with non-haemolytic streptococci
Pleural fluid	Lower respiratory tract infections (bacterial pneumonia, lung abscess, bronchiectasis)	α-haemolytic streptococci (*S. pneumoniae*), β-haemolytic streptococci (*S. pyogenes*), non-haemolytic streptococci (Enterococci and non enterococcal streptococci), *Staphylococcus aureus, Staphylococcus epidermidis,* (**Gram-positive cocci**); *Escherichia coli, Klebsiella, Haemophillus influenzae, Salmonella* (**Gram-negative bacilli**)	Very strong association with *Staphylococcus aureus* and *Streptococcus pneumoniae;* Strong associations with, non-haemolytic streptococci, *E. coli Klebsiella and Salmonella;* Moderate associations with *Streptococcus pyogenes, streptococcus epidermidis* and *H. influenzae.*
Ear swab	Ear infections	*Staphylococcus aureus, Staphylococcus epidermidis,* non-haemolytic	Very strong association with

		streptococci (Enterococci), α-haemolytic streptococci (*S. pneumoniae*) β-haemolytic streptococci (*S. pyogenes*) (**Gram-positive cocci**); *Proteus* spp, *Pseudomonas* spp, *Klebsiella* spp, *Escherichia coli*, (**Gram-negative bacilli**); *Corynebacterium* spp.	*Staphylococcus aureus,* Strong associations with *Pseudomonas and Proteus* spp. Moderate associations with *E. coli, Klebsiella,* non-haemolytic *streptococci.* Weak associations with *S. pneumoniae, S. pyogenes and Corynebacterium* spp .
Throat swab	Upper respiratory tract infections	*Staphylococcus aureus*, α-haemolytic streptococci (*S. pneumoniae*) β-haemolytic streptococci (*S. pyogenes*), non-haemolytic streptococci (Enterococci), **(Gram-positive cocci)**; *Proteus* spp, *Pseudomonas* spp, *Klebsiella* spp (**Gram-negative bacilli**)	Very strong associations with non-haemolytic streptococci , Streptococcus pyogenes, Streptococcus pneumoniae, and *Staphylococcus aureus.* Weak associations with *Klebsiella, Proteus, Pseudomonas* spp
Eye swab	Eye infections	*Staphylococcus epidermidis, Staphylococcus aureus* α-haemolytic streptococci (*S. pneumoniae*), β-haemolytic streptococci (*S. pyogenes*) non-haemolytic streptococci (Enterococci), (**Gram-positive cocci**) *Neisseria spp.* (**Gram-negative cocci**)	Very strong associations with *Staphylococcus epidermidis* and moderate associations *Staphylococcus aureus* and S. pneumoniae, S pyogenes, non-haemolytic streptococci
Pus swab	Wound infections	*Staphylococcus aureus*, *Staphylococcus epidermidis,* α-haemolytic streptococci (*S. pneumoniae*) β-haemolytic streptococci (*S. pyogenes*), non-haemolytic streptococci (Enterococci), **(Gram-positive cocci)** *Escherichia coli, Klebsiella* spp, *Proteus* spp, *Pseudomonas* spp, *Acinetobacter* (**Gram-negative bacilli**).Neisseria spp (**Gram-negative cocci**) Peptococcus, and Bacteroides (**Anaerobic organisms**)	Very strong association with *Staphylococcus aureus*. Strong associations with *E. coli, Proteus, Pseudomonas* and *Klebsiella.* Weak associations Weak associations with *Staphylococcus epidermidis Streptococcus pyogenes*, non-

			haemolytic streptococci, *Streptococcus pneumoniae*
Blood	Septicaemia	*Staphylococcus aureus*, *Staphylococcus epidermidis*, non-haemolytic streptococci (Enterococci), α-haemolytic streptococci (*S. pneumoniae*) (**Gram-positive cocci**); *Proteus* spp, *Pseudomonas* spp, *Klebsiella* spp, (**Gram-negative bacilli**);	All organisms strongly associated, particularly *Staphylococcus aureus* and *Proteus* spp and also, *Staphylococcus epidermidis Streptococcus pneumoniae*, non-haemolytic streptococci, *Klebsiella* and *Pseudomonas* spp.
Sputum	Respiratory tract infections	*Staphylococcus aureus, Staphylococcus epidermidis,* α-haemolytic streptococci (*S. pneumoniae*), β-haemolytic streptococci (*S. pyogenes*), non-haemolytic streptococci (Enterococci), (**Gram-positive cocci**); *Klebsiella, Escherichia coli, Haemophillus influenzae, Haemophillus parainfluenzae Pseudomonas* (**Gram-negative bacilli**)	Strong associations with *Staphylococcus aureus*, *Streptococcus pneumoniae, and Klebsiella*
Urine	Uncomplicated urinary tract infections	*Escherichia coli, Klebsiella* spp, *Proteus* spp, *Pseudomonas* spp (**Gram-negative bacilli**); *Staphylococcus aureus*, *Staphylococcus epidermidis,* α-haemolytic streptococci (*S. pneumoniae*), non-haemolytic streptococci (Enterococci), β-haemolytic streptococci (*S. pyogenes*) (**Gram-positive cocci**) *Peptococcus* spp, *Bacteroides* spp. (**Anaerobic bacteria**)	Very strong association with *E. coli*. Strong association with *Klebsiella* spp. Moderate associations with *Proteus* spp, *Pseudomonas, Staphylococcus aureus*, non-haemolytic streptococci (enterococci) Very weak associations with other gram-positive cocci including *Staphylococcus saprophyticus, Staphylococcus epidermidis Streptococcus pyogenes* and *Streptococcus pneumoniae*
Penile discharge	Urethritis	*Staphylococcus aureus, Staphylococcus epidermidis,* α-haemolytic	Very strong association with

		streptococci (*S. pneumoniae*) (**Gram-positive cocci**); *Escherichia coli*, *Klebsiella* spp *Pseudomonas* spp (**Gram-negative bacilli**) *Neisseria spp* (**Gram-negative cocci**) Corynebacterium	*Staphyloccocus aureus*. Moderate associations with *Staphyloccocus epidermidis, Streptococcus pneumoniae. Escherichia coli, Klebsiella* spp, *Pseudomonas* spp. *Corynebacterium* spp.
High vaginal swab	Cervicitis	*Staphylococcus aureus, Staphylococcus epidermidis,* non-haemolytic streptococci (Enterococci), α-haemolytic streptococci (*S. pneumoniae*) β-haemolytic streptococci (*S. pyogenes*) (**Gram-positive cocci**); *Proteus* spp, *Pseudomonas* spp, *Klebsiella* spp, *Escherichia coli*, *Salmonella* spp (**Gram-negative bacilli**) *Neisseria spp* (**Gram-negative cocci**) Peptococcus (**Anaerobic organism**)	Very strong association with *Staphyloccocus aureus.* Moderate associations with *Escherichia coli*, Klebsiella spp *Proteus* spp, *Streptococcus pyogenes* and non-haemolytic streptococci (enterococci), Very weak associations with *Salmonella*, *Peptococcus Pseudomonas* and *S. pneumonia*

4.2.3 Sensitivities and variations in yearly percentage resistance of bacterial pathogens to formulary antibiotics - January 2000 - Dec 2005

The section reports results of analysis of pooled data of culture sensitivity test (CST) results from study sites to determine the extent of pathogens' sensitivities or resistances to formulary or currently used antibiotics at study site hospitals. Sensitivities of major bacterial isolates as reported by laboratories to said antibiotics within the specified period of data collection were stated and discussed within noted limitations of this step of the study and trends of general sensitivity patterns to antibiotics as provided in the literature. Two third generation cephalosporins (TGCs), cefotaxime and ceftriaxone were used in culture sensitivity testing. The frequencies of testing pathogens against either antibiotic were few and on the basis of the existence cross-resistance among the TGCs (Chan *et al.* 1999:58) sensitivity data on the two antibiotics were combined and reported as one antibiotic -TGC (cefotaxime and ceftriaxone). TGCs as indicated in these presentations should be interpreted as cefotaxime and ceftriaxone except where used as literature derived information when it TGC would then be referring all cephalosporins classified in the literature as third-generation cephalosporins.

4.2.3.1 Bacterial isolates and their reported patterns of sensitivities to formulary antibiotics

4.2.3.1.1 Results

- **Bacterial isolates**

Tables 4.2.4 and 4.2.5 respectively provide calculated sensitivities of gram-positive and gram-negative bacterial isolates to formulary antibiotics between January 2000 and June 2006. Bacterial pathogens regularly isolated and tested against formulary antibiotics included in the respective categories of gram-positive and gram-negative bacteria,

- *Streptococcus pyogenes* (β-haemolytic streptococci), *Streptococcus pneumoniae* (α-haemolytic streptococci) non-haemolytic streptococci (enterococci), *Staphylococcus aureus* and *Staphylococcus epidermidis* (Gram-positive cocci)
- *Escherichia coli, Klebsiella spp* and *Proteus spp* and *Pseudomonas spp.* [gram-negative bacteria (GNB)]

Table 4.2.4 Percentage sensitivities of gram-positive cocci/bacilli isolates to formulary antibiotics - January 2000 - June 2006

Bacterial isolates	**Frequencies of tests (T), sensitivities (S) and percentage sensitivities (%S) of bacterial isolates to formulary antibiotics**																	
	Ampicillin			Penicillin			Methicillin/Cloxacillin			Erythromycin			Tetracycline			Co-trimoxazole		
	T	S	%S	T	S	%S	T	S	%S	T	S	%S	T	S	%S	T	S	%S
β-Haemolytic streptococci (*Streptococcus . pyogenes)*	100	81	81	81	49	60.5	11	9	80	84	51	60.7	95	53	56	73	15	20.5
α-Haemolytic streptococci (*S. pneumoniae)*	97	87	89.7	62	48	77.4	9	6	66	88	68	77.3	85	61	72	61	40	66
Non-haemolytic streptococci (enterococci)	145	103	71.0	106	51	48.1	2	1	50	113	67	59.3	138	70	51	112	36	32.1
S. aureus	1196	470	39.3	998	235	23.5	392	276	70	777	523	67.3	1121	523	47	872	337	38.6
S. epidermidis	97	47	48.5	51	16	31.4	12	6	50	88	41	46.6	64	21	33	76	24	31.6
S. saprophyticus	4	2	50	0	0	0	0	0	0	0	0	0	4	1	25	0	0	0
Corynebacterium spp	7	5	71.4	4	3	75	0	0	0	7	2	28.6	8	4	50	6	3	50
	Chloramphenicol			Ciprofloxacin			TGC											
	T	S	%S	T	S	%S	T	S	%S									
β-Haemolytic streptococci (*Streptococcus . pyogenes)*	19	8	42.1	1	1	100	11	9	81.8									
α-Haemolytic streptococci (*S. pneumoniae)*	30	26	86.7	10	8	80	16	12	75									
Non-haemolytic streptococci (enterococci)	61	45	73.8	1	1	100	21	19	90.5									
S. aureus	544	350	64.3	168	122	73	349	255	73.1									
S. epidermidis	42	23	54.8	18	15	83	26	18	69.2									
S. saprophyticus	4	2	50	0	0	0	0	0	0									
Corynebacterium spp	4	2	50	2	1	50	1	1	100									

Table 4.2.5 Percentage sensitivities of gram-negative bacilli/cocci isolates to formulary antibiotics - January 2000 - June 2006

Bacterial isolates	**Frequencies of tests (T), sensitivities (S) and percentage sensitivities (%S) of bacterial isolates to formulary antibiotics**																	
	Ampicillin			Co-trimoxazole			Tetracycline			Chloramphenicol			Ciprofloxacin			TGC		
	T	S	%S	T	S	%S	T	S	%S	T	S	%S	T	S	%S	T	S	%S
Acinetobacter spp	5	1	20	11	1	9.09	3	1	33	12	2	16.7	12	8	67	10	3	30
Enterobacter spp	2	0	0	0	1	0	0	0	0	2	2	100	3	3	100	4	3	75
Escherichia coli	1659	265	16.0	621	220	35.4	1211	384	32	1462	837	57.3	285	221	78	494	436	88.3
H. influenzae	4	2	50	3	0	0	4	4	100	4	4	100	0	0	0	1	1	100
H. parainfluenzae	0	0	0	0	0	0	1	1	100	1	0	0	1	0	0	1	1	100
Klebsiella spp	481	84	17.5	303	96	31.7	263	96	37	384	205	53.4	140	103	74	249	122	49
Pseudomonas spp	101	16	15.8	69	13	18.8	26	8	31	100	39	39	217	196	90	121	92	76
Proteus spp	414	116	28.0	378	89	23.5	108	20	19	463	220	47.5	156	141	90	399	364	91.2
Neisseria spp	15	6	40	8	2	25	10	9	90	2	1	50	2	1	50	1	1	100
Peptococcus spp	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Bacteroides spp	0	0	0	0	0	0	0	0	0	0	0	0	1	1	100	0	0	0
Salmonella spp	0	0	0	0	0	0	0	0	0	0	0	0	3	2	67	3	2	66.7
Shigella spp	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	2	1	50

Table 4.2.5 continues:

Bacterial isolates	Frequencies of tests (T), sensitivities (S) and percentage sensitivities (%S) of bacterial isolates to formulary antibiotics																	
	Gentamicin			Amikacin			Nalidixic acid			Nitrofurantoin								
	T	S	%S	T	S	%S	T	S	%S	T	S	%S						
Acinetobacter spp	11	6	54.5	8	7	88	0	0	0	0	0	0						
Enterobacter spp	4	3	75	3	3	100	0	0	0	0	0	0						
Escherichia coli	1617	1260	77.9	142	127	89	950	771	81.2	921	792	86						
H. influenzae	4	4	100	0	0	0	0	0	0	0	0	0						
H. parainfluenzae	0	0	0	0	0	0	0	0	0	0	0	0						
Klebsiella spp	429	305	71.1	95	89	94	199	154	77.4	196	144	73						
Pseudomonas spp	199	183	92	187	176	94	8	6	75	9	4	44						
Proteus spp	466	369	79.2	107	39	36	43	33	76.7	44	10	23						
Neisseria spp	5	3	60	1	1	100	0	0	0	0	0	0						
Peptococcus spp	0	0	0	0	0	0	0	0	0	0	0	0						
Bacteroides spp	0	0	0	0	0	0	0	0	0	0	0	0						
Salmonella spp	0	0	0	2	2	100	0	0	0	0	0	0						
Shigella spp	0	0	0	2	2	100	0	0	0	0	0	0						

ABBREVIATIONS USED IN TABLE: T, S and %S respectively indicate number of organisms tested against antibiotic, number sensitive to antibiotic, and calculated percentage sensitivity of organism to antibiotic

Pathogens less isolated and least tested against formulary antibiotics included

- *Staphylococcus saprophyticus* and *Corynebacterium* spp among gram-positive bacterial isolates;
- *Acinetobacter* spp, *Enterobacter* spp, *Haemophillus influenzae*, *Haemophilus parainfluenzae*, *Shigella* spp and *Salmonella* spp among gram-negative bacteria; and
- *Peptococcus* spp and *Bacteroides* spp among anaerobic bacteria.

- **Antibiotics and morphological classifications of bacterial pathogens regularly tested against them**

By practice laboratories tested gram-positive and gram-negative bacteria respectively against the following groups of antibiotics:

- **Gram-positive bacteria**: Ampicillin, penicillin, erythromycin, cloxacillin, tetracycline/doxycycline, co-trimoxazole chloramphenicol ciprofloxacin and third generation cephalosporins (TGCs).
- **Gram-negative bacteria**: Ampicillin, co-trimoxazole, tetracycline chloramphenicol, ciprofloxacin, TGCs, gentamicin, amikacin, nalidixic acid and nitrofurantoin.

- **Sensitivities of bacterial isolates to formulary antibiotics**

- **Gram-positive bacteria**

Percentage sensitivities of the major gram-positive bacteria isolated and tested against indicated antibiotics are reported as follows:

- ***Streptococcus pyogenes*** (β-haemolytic streptococci) demonstrated highest percentage sensitivities of 81%, 80% and 82% respectively to ampicillin, methicillin/cloxacillin and TGCs (cefotaxime/ceftriaxone); intermediate sensitivities of 60%, 61% and 56% towards penicillin, erythromycin and tetracycline and low sensitivities of 21% and 42% to co-trimoxazole and chloramphenicol. The organism was found to be sensitive to ciprofloxacin for the one time that it was tested against the antibiotic.

- ***Streptococcus pneumoniae*** (α-haemolytic streptococci) generally showed sensitivities of between 72% and 90% towards antibiotics against which they had been tested. Specifically they were found to be 90% sensitive to ampicillin, 77% sensitive to penicillin and erythromycin, 72% sensitive to tetracycline, 87% sensitive to chloramphenicol, 80% sensitive to ciprofloxacin and 75% sensitive to the TGCs. The pathogens demonstrated their lowest sensitivities of 66% to both methicillin/cloxacillin and co-trimoxazole.

- **Non-haemolytic streptococci** (non-enterococci and enterococci - *Enterococcus faecalis*, *Enterococcus faecium*) showed sensitivity rates of 71%, 74%, and 90% to ampicillin, chloramphenicol and TGCs. They demonstrated low sensitivity rates of 32%, 40%, 51% and 51% to co-trimoxazole, penicillin, tetracycline and erythromycin respectively. They were found to be sensitive once out of the two times that they were tested against methicillin/cloxacillin and also sensitive for the one time that it was tested against ciprofloxacin.

- ***Staphylococcus aureus*** showed similar sensitivity rates of 70% and 73% each respectively to methicillin/cloxacillin, ciprofloxacin and the TGCs. Sensitivities of the organism to other antibiotics were determined as 24% for penicillin, 39% for both ampicillin and co-trimoxazole, 64% for chloramphenicol and 67% for erythromycin.

- ***Staphylococcus epidermidis*** in the exception of ciprofloxacin towards which it showed a comparatively high sensitivity rate of 83%, generally demonstrated low sensitivities to many antibiotics including its show of 31% sensitivity to penicillin and 32%, 33%, 40%, 47% 50%, 55% and 69% sensitivities respectively to co-trimoxazole, tetracycline, ampicillin, erythromycin, methicillin/cloxacillin, chloramphenicol and the TGCs.

- Isolates of ***Staphylococcus saprophyticus*** were tested four times only against ampicillin, chloramphenicol and tetracycline and for this number of times that it was tested against the antibiotics the organism was found to be sensitive once (25% sensitivity) towards tetracycline and twice each (50% sensitivity) towards ampicillin and chloramphenicol.

- ***Corynebacterium*** spp isolates were found to be sensitive once towards ciprofloxacin out of two times that they were tested against the antibiotic and sensitive once to a TGC for the one time that it was tested against this class of antibiotics. For the few times (4 - 8 times) that the pathogens were tested against other antibiotics they were found to demonstrate sensitivities of 71.3%, 75%, and 28.6% respectively towards ampicillin, penicillin and erythromycin and 50% in each case towards tetracycline, co-trimoxazole, chloramphenicol.

- **Gram-negative bacteria**

In the exception of few a deviations observed with individual pathogens in the morphological grouping, gram-negative bacilli (GNB) generally demonstrated antibiotic sensitivity patterns in which the organisms were seen to exhibit low sensitivities to ampicillin, co-trimoxazole, tetracycline and chloramphenicol on one hand and high sensitivities to the quinolones (ciprofloxacin and nalidixic acid), TGCs (cefotaxime and ceftriaxone) and the aminoglycosides (gentamicin and amikacin) on the other hand. Specific sensitivity patterns shown by individual members of the morphologic grouping are as outlined below.

- ***Escherichia coli*:** The pathogen exhibited sensitivity rates of 16%, 32%, 35%, and 57% respectively towards ampicillin, tetracycline, co-trimoxazole and chloramphenicol, 78% towards ciprofloxacin and gentamicin, and 81%, 86%, 88% and 89% respectively towards, nalidixic acid, nitrofurantoin, TGCs and amikacin.

- ***Klebsiella* spp:** *Klebsiella* demonstrated sensitivity rates of 17% sensitive to ampicillin, 32% to co-trimoxazole, 37% to tetracycline and 49% to the TGCs. Their sensitivities to gentamicin, nitrofurantoin, ciprofloxacin, nalidixic acid and amikacin in that order were 71%, 73%, 74%, 77%, and 94%.

- ***Proteus* spp:** The organisms were found to be 19% sensitive to tetracycline, 23% sensitive to nitrofurantoin and 28%, 24% and 48% sensitive respectively to ampicillin, co-trimoxazole and chloramphenicol. They demonstrated low sensitivity rates of 36% to amikacin unlike other enteric GNB and

comparatively high percentage sensitivities of 77%, 79%, 90% and 91% to nalidixic acid, gentamicin, ciprofloxacin and the TGCs.

- ***Pseudomonas* spp:** *Pseudomonas* exhibited low sensitivity rates of 16%, 19%, 31%, 39% and 44% towards ampicillin, co-trimoxazole, tetracycline, chloramphenicol and nitrofurantoin and appreciably high sensitivities of 92% and 94% towards the aminoglycosides gentamicin and amikacin, 90% and 74% towards the quinolones ciprofloxacin and nalidixic acid and 76% towards the TGCs (cefotaxime and ceftriaxone).

- **Rare gram-negative bacterial isolates:**
  Acinetobacter: For the few times that *Acinetobacter* spp were cultured and tested against prescribed antibiotics, the pathogens were found to demonstrate an appreciably high sensitivity rate of 88% towards amikacin and a middle range sensitivity of 54% and 67% to gentamicin and ciprofloxacin. It displayed high resistances to all other antibiotics including its show of sensitivities of 20% to ampicillin, 9% to co-trimoxazole, 33% to tetracycline, 16% to chloramphenicol and 30% to TGCs (ceftriaxone and cefotaxime).

  ***Neisseria* spp**: The pathogens demonstrated sensitivities of 90% towards tetracycline, 60% towards gentamicin, 40% towards ampicillin and 25% co-trimoxazole for the few times that they were also cultured and tested against formulary antibiotics. For one out of the two times each that the organisms were tested against chloramphenicol and ciprofloxacin they were found to be sensitive towards these antibiotics. *Neisseria* spp were also tested once against amikacin and TGC and were found to be sensitive.

  Haemophilus influenzae demonstrated 50% sensitivity to ampicillin and 100% sensitivities each to tetracycline, chloramphenicol and gentamicin for the four times that they were tested against these antibiotics. The organisms showed 100% resistance to co-trimoxazole for the three times that they were tested against the antibiotic.

Salmonella spp were seen to be 67%, 66% and 100% sensitive to ciprofloxacin, TGCs and amikacin for the three times that they were tested against these antibiotics.

Shigella spp exhibited 50% and 100% sensitivities to ciprofloxacin and amikacin for the two times that isolates of the pathogens were tested against these antibiotics.

- **Anaerobic bacterial isolates**, *Peptococcus* and *Bacteroides* spp had generally not been tested against formulary antibiotics. *Bacteroides* spp were tested only once against ciprofloxacin and were found to be sensitive.

4.2.3.1.2. Results Evaluation and Discussion

- **Limitations in data collection for bacterial pathogen antibiotic sensitivity determinations**

A number of limitations associated with the step of the research involving bacterial pathogen antibiotic sensitivity determinations and which have been thought to compromise the quality of data used for these determinations have been noted. Principal among these are included the following:

- Random determinations by site laboratories of antibiotics used in culture sensitivity testing each time pathogens are isolated. This was seen to be done instead of following routines in which all antibiotics regularly used in treating infections of given bacterial isolates are tested against such isolates each time they are isolated. The practice gave rise to certain pathogens being tested for much fewer times against certain antibiotics as compared with the frequencies of isolation of such pathogens and their testing against other antibiotics. The effect of the limitation is to produce data in which frequencies of isolations of pathogens vary greatly with the number of times they are tested against different antibiotics and making organisms' observed sensitivity or resistant patterns to various antibiotics, if compared, less precise than would have been the case in absence of the limitation.

- The identification of bacterial isolates by species or group names and the reporting of organisms' antibiotic sensitivities as such group or species characteristics. The limitation made it impossible in some cases to associate reported antibiotic sensitivity patterns to specific organisms and is thought to compromise data quality and adequate interpretation of results.

These limitations withstanding, it is important to mention that organisms' percentage sensitivities to given antibiotics were determined as ratios of frequencies of the number of times they were found sensitive to the number of times they were tested against given antibiotics. On the basis of this, pathogens' percentage sensitivities as determined were considered as still providing authentic information on the sensitivity or resistance patterns of the tested organisms to the given antibiotics against which they were tested, even if such tests were performed for a few times.

Having said this though, calculated percentage sensitivities of bacterial isolates to given antibiotics are taken into consideration for data analysis only if such isolates are tested for a large enough number of times. This is done for reasons of the fact that statistical authenticity of results of this kind of study in which calculated values forming part of data analysed are based on frequencies of occurrences of events, depends on sample size with larger samples providing more statistically significant or authentic results (Utts & Heckard, 2007:720).The study considered for this purpose and because of the nature of data being analysed, pathogen test frequencies of at least 8 (eight) to make percentage sensitivity or resistant calculations for organisms valid for consideration in determining the pattern of the organism's sensitivities towards antibiotics against which it had been tested.

- **Pathogen antibiotic sensitivity patterns: Gram-positive cocci**

- ***Streptococcus pneumoniae* (*S. pneumoniae*, pneumococci or α-haemolytic streptococci)**

S. pneumoniae resistance to the β-lactam and other antibiotics have been reported by many studies as noted in the literature review chapter of this thesis to be increasing globally (Section 2.1.4.1).

By the year 2000, these global increases in the organisms' development of resistance were reported to have reached 24.6% for penicillin and erythromycin (Blasi *et al.* 2006:363) which by comparison is similar to the 23% rates of resistances of the organisms to penicillin and erythromycin reported by this study. In 1999, SENTRY, an antibiotic resistance surveillance group in Europe similarly reported a 25% resistance rate of *Streptococcus pneumoniae* to tetracycline which was current for that year but without much deviation from what had been in previous two years (Johnson *et al.*, (2001:S7). By comparison, the 28% rate of resistance reported by this study as the rate of resistance of *S. pneumoniae* to tetracycline by the end of the year 2005 in Lesotho is considered similar to that reported by the European antibiotic resistance surveillance group (Johnson *et al.*, (2001:S7) The seemingly comparable rates of resistances reported by this study and other studies that were conducted worldwide as reported in Section 2.1.4.1 has the significance of authenticating results of this study to such a degree as to make determined patterns of sensitivities of *S. pneumoniae* to antibiotics against which they have been tested acceptable in spite of the limitations thought of as affecting the reliability of results as indicated above.

Penicillin-susceptible and most penicillin intermediate resistant strains of pneumococci are susceptible to TGCs including cefotaxime and ceftriaxone while about fifty per cent of these pathogens highly resistant to penicillin are resistant to these antibiotics and also cefepime (Musher, 2005:811). Lower resistant rates of *S. pneumoniae* to TGCs are for this reason expected contrary to the reported 25% resistance of the organisms to the antibiotics, which is in the same range as the organisms' 23% resistance rate reported for penicillin as results of the study depicted. While factors deemed as limiting the accuracy of results of this study as indicated above may offer an explanation to this observation, it is also most probable that strains of the organism found to be resistant to penicillin are more of the highly than intermediate penicillin resistant strain types of the organism. This finding, though remaining hypothetical until proved by further research work, tends to suggest that penicillin resistant strains of *Streptococcus pneumoniae* in hospitals in Lesotho, particularly the Queen II Hospital where more than 80% of culture sensitivity test data analysed for this study were obtained are mainly the highly penicillin resistant strains of the organism which have high propensity of being resistant to cephalosporins including as well the TGCs. This observation negates the empiric

prescription of TGCs in the treatment of pneumococcal infections unresponsive to penicillin treatment.

Antibiotics with high activities against pneumococcal infections presenting at study site hospitals were found to be ampicillin, chloramphenicol and ciprofloxacin (Table 4.2.4). The activity of ciprofloxacin against *Streptococcus pneumococci* was comparable to those of ampicillin, chloramphenicol and erythromycin, despite the antibiotic's literature documented moderate activities against cocci and the prohibition of its use for this reason in treating pneumococcal pneumonia (British Medical Association & Royal Pharmaceutical Society of Great Britain, 2003:294). *Streptococcus pneumoniae* was tested against ciprofloxacin only 10 times and its determined sensitivity of 80% against the antibiotic may not be taken as a *de facto* result that could change the recommendation of the non-use of the antibiotic in treating pneumococcal infections among the study population. The more recent fluoroquinolones e.g. moxifloxacin are reported to be highly effective against pneumococci (Musher, 2005:811) and can be used instead of ciprofloxacin in treating the infections.

Co-trimoxazole and cloxacillin exhibited the lowest rates of activity against *Streptococcus pneumoniae*. By reported results, the pathogen exhibited 44% resistance towards both antibiotics. The organism, according to Musher (2005:811), exhibits about 33.3% resistance towards co-trimoxazole, a resistance rate which comparably confirms the high 44% resistance rate of the pathogens against the antibacterial agent in Lesotho. Co-trimoxazole is predominantly prescribed in respiratory tract infections where *S. pneumoniae* is associated causative agent (Tables 4.1.15 and 4.2.2). By these findings co-trimoxazole is not considered an antibiotic of choice in the empiric treatment of pneumococcal infections and its predominant use in the empiric treatment of respiratory tract infections with pneumococci as aetiological agents among the study population should be avoided.

- ***Streptococcus pyogenes* (*S. pyogenes*, β-haemolytic streptococci)**

S. pyogenes, by literature findings are known to exhibit high sensitivities to a number of antibiotics including penicillin, other β-lactam antibiotics and the fluoroquinolone levofloxacin to which they exhibit 100% susceptibility (Nguyen & Chung, 2005:1145; Felmingham *et al.,* 2004:49) and also the macrolide antibiotics erythromycin,

clarithromycin and azithromycin to which they are seen to be approximately 90% sensitive to the macrolide antibiotics (Felmingham *et al.,* 2004:49).

In comparison with literature reported antibiotic susceptibility patterns of *S. pyogenes* as indicated, and with their exhibition of resistances of between 18% (ampicillin) and 39.5% (penicillin and erythromycin) against the β-lactam antibiotics and erythromycin (Table 4.2.4) it can be said that isolates of the pathogen in Lesotho have developed resistances to antibiotics generally recommended for the empiric treatment of *S. pyogenes* infections to levels high enough to obliterate expected therapeutic benefits of the use of these antibiotics in treating these infections. Wessels (2005:825-826) for example recommended the use of penicillin or erythromycin in the cases of penicillin-sensitive individuals in treating *S. pyogenes* infections and the antibiotics according to study results (Results: Section 4.1.2.5, Table 4.1.35) are among antibiotics most likely to be prescribed as single antibiotic therapies in outpatient departments in the treatment of respiratory tract and soft tissue infections for which *S. pyogenes* are associated aetiological agents. The reported 39.5% resistance levels of *S. pyogenes* against penicillin and erythromycin precludes the use of these antibiotics in the empiric treatment of *S. pyogenes* infections.

- **Non-haemolytic streptococci (Enterococci and non-enterococcal streptococci)**

Non-haemolytic streptococci are composed of species of streptococci that include enterococci and non enterococcal streptococci. These species from a search of literature (Section 2.1.4.1) characteristically demonstrate different sensitivity patterns to antibiotics and the reporting of culture sensitivity test results by laboratories as characteristic properties of this classification of streptococci without indications of which members of the group such results apply to, made it impossible to associate reported antibiotic sensitivities for the classification to specific pathogens that actually exhibit them. This is a limitation of the study as indicated in an earlier paragraph and its effect on data quality and analysis is observed in the interpretation of reported antibiotic sensitivities for this group of streptococci.

Among the group of non-haemolytic streptococci and as reviewed in the literature (Section 2.1.4.1), non-enterococcal streptococci exemplified by *Streptococcus bovis,* and anaerobic streptococci (*Peptococcus* and *Peptostreptococcus* spp), are reported to be usually susceptible to penicillin and many other antibacterial agents. The enterococci

members of the group , principally *Enterococcus faecalis*, *Enterococcus faecium* on the other hand are known to have intrinsic resistance to penicillins, the aminoglycosides and lincosamides as well as having high propensity to developing acquired resistance to other agents including the macrolides, tetracyclines, chloramphenicol, quinolones and the glycopeptides (Johnson *et al.,* 2001:S7). With these reports of intrinsic resistances and susceptibilities of enterococci and non- enterococcal streptococci members of the non-haemolytic streptococci to penicillins and the high propensity of enterococci developing resistance to other antibiotics one could interpret the reported high resistances of 52%, 68%, 49% and 41% of non-haemolytic streptococci respectively for penicillin, co-trimoxazole, tetracycline and erythromycin (Table 4.2.4) as indicating *Enterococcus* spp as the major isolates reported as non-haemolytic streptococci. On the assumption of such indication being correct it could be reasonably presumed that enterococci are appreciably sensitive to ampicillin, chloramphenicol and TGCs amidst reports of non-haemolytic streptococci isolates being respectively sensitive to these antibiotics at rates of 71%, 74% and 91% (Table 4.2.4). Having stated this though, the high probability of enterococci being resistant to most antibiotics precludes the reliance on empiric prescriptions for the treatment of infections by these organisms.

- ***Staphylococcus aureus (S. aureus)***

S. aureus is largely penicillinase producing and majority strains of the pathogen are for this reason intrinsically resistant to the penicillins (Lowy, 2005:821). The author indicated greater than 95% of the pathogen being of strains that produce the enzyme and by prediction, about this percentage (>95%) of isolates of the pathogen are expected to be resistant to penicillins other than the semisynthetic penicillinase resistant penicillins (SPRPs) which include for example methicillin, cloxacillin, dicloxacillin, flucloxacillin and nafcillin. The exhibition of 23% and 39% sensitivities of *S. aureus* to penicillin and ampicillin respectively rather indicates a much higher percentage (23% to 39%) than the less than 5% of *S. aureus* isolates indicated by (Lowy, 2005:821) to be non-penicillinase producing. This indicates a significantly higher than literature indicated proportion of isolates of *S. aureus* that are penicillin sensitive strains of the pathogen. The therapeutic usefulness of this finding with respect to empiric prescription of non-semisynthetic penicillinase resistant penicillins (non-SPRPs) in treating *S. aureus* infections is, however obliterated by the fact that until a culture sensitive test is done, it is impossible to distinguish penicillin sensitive from penicillin resistant strains of the pathogen as

implicating agents of an infection to enable a choice of a non-SPRP to be made for the empiric treatment of such infections.

S. aureus also exhibited a 30% resistance rate to methicillin/cloxacillin which by interpretation also indicates the approximate fraction of MRSA strains present among *S. aureus* isolates tested for their antibiotic sensitivities at study sites. According to Lowy (2005:821) MRSA strains form about 40 – 50% of all isolates of *S. aureus* in many hospitals. On the basis of this the 30% of total isolates of the pathogen estimated as being the MRSA percentage component of total isolates of *S. aureus* in the major hospitals in Lesotho is considered significant therapeutically as it predicts better treatment outcomes of *S. aureus* infections treated with SPRPs in comparison with what would have been the case if literature indicated the MRSA percentage component of total isolates of *S. aureus* were seen to be prevailing in hospitals in Lesotho.

The majority of MRSA cross-resistance with other antibiotics including the cephalosporins, the quinolones, aminoglycosides and macrolides (Jones *et al.*, 2003:408), creating as a result a sensitivity pattern in which methicilin susceptible *Staphylococcus aureus* (MSSA) strains of *S. aureus* are seen to be sensitive to these other antibiotics while MRSA strains are seen to be resistant to them. In spite of limitations cited in the data collection for this step of the study as indicated in the opening paragraphs of this Section (Section 4.2.3.1.2), predictable resistances of 27% of *S. aureus* to TGCs and ciprofloxacin which are similar to the percentage resistance of 30% of *S. aureus* to methicillin/cloxacillin were determined for these two antibiotics. As an implication of this finding, cloxacillin cannot be substituted for TGCs or quinolones (ciprofloxacin) in the event of treatment failures following the empiric prescription of the antibiotic in treating staphylococcal infections.

Contrary to literature findings indicating that MRSAs are sensitive to co-trimoxazole at a rate of ≥70% (Jones *et al.,* 2003:408) results of this study showed *S. aureus* demonstrating a relatively high 61% resistance to the antibiotic, a resistance rate which negates the prescription of the antibiotic in treating staphylococcal infections at study site hospitals. The pathogen also showed high resistance rates to other regularly prescribed antibiotics including penicillin (76%), ampicillin (61%), tetracycline (53%) chloramphenicol (36%) and erythromycin (33%) to also negate the use of any of these

antibiotics as a first choice over cloxacillin or an empiric substitution of it in the treatment of *Staphylococcus aureus* associated infections.

- ***Staphylococcus epidermidis* (*S. epidermidis*)**

Staphylococcus epidermidis, according to literature findings are often resistant to semisynthetic penicillinase resistant penicillins (SPRP) particularly isolates from hospital patients (Elliot 2004:28). Predictably and on the basis of this antibiotic's sensitivity characteristic property of the pathogen, *S. epidermidis* isolates were seen to demonstrate a low 50% sensitivity to methicillin/cloxacillin. Except for comparatively lower resistances of 17% and 31% respectively demonstrated by the organisms towards ciprofloxacin and the TGCs *S. epidermidis* generally exhibited high rates of resistance towards most antibiotics against which they were tested including penicillin (69%), co-trimoxazole (68%), tetracycline (67%), ampicillin (60%), erythromycin (53%) and chloramphenicol (45%).

The trend of antibiotic sensitivity patterns seen with the staphylococci precludes the use of any currently available antibiotics in the empiric treatment of *Staphylococcus aureus* and *Staphylococcus epidermidis* infections following treatment failures with cloxacillin in cases of *Staphylococcus aureus* infections or with ciprofloxacin in cases of *Staphylococcus epidermidis* infections. This necessitates the introduction of an antibiotic into the Lesotho national formulary for use as a second choice antibiotic in the treatment of staphylococci infections unresponsive to the semisynthetic penicillinase resistant antibiotics. Literature findings have shown both MRSA and *Staphylococcus epidermidis* to be very susceptible to the glycopeptide, vancomycin (Jones *et al.* 2003:408). The antibiotic is neither currently used in Lesotho nor tested against organisms in culture sensitivity tests and despite current reports of isolation of vancomycin resistant strains of *Staphylococcus aureus* in certain parts of the world (Appelbaum, 2007:399) the antibiotic is recommended for procurement and use in cases of MRSA infections.

- **Pathogen antibiotic sensitivity patterns: Gram-negative bacilli (GNB)**

- ***Escherichia coli* (*E. coli*)**

Patterns of sensitivity demonstrated by *Escherichia coli* to formulary antibiotics against which the organisms were tested generally followed trends reported in the literature

(Section 2.1.5.2.1). The pathogen is β-lactamase producing as literature findings indicate and is predictably highly resistant to ampicillin against which it reportedly exhibits a resistance rate of 84%. It also showed high resistances to tetracycline (68%) and chloramphenicol (43%) and to co-trimoxazole (65%) (Table 4.2.5), antibiotics for which increasing rates of resistance development of the organism in the United States, Europe and the developing countries have been reported in the literature (Section 2.1.5.2.1). Compared to other antibiotics and in line with further literature reports, the pathogen was seen to exhibit comparatively lower resistances to TGCs (ceftriaxone and cefotaxime), the aminoglycosides (gentamicin and amikacin), the quinolones (ciprofloxacin and nalidixic acid) and nitrofurantoin. It, however, showed higher rates of resistance to these antibiotics, ranging from 11% for amikacin to 22% for gentamicin and ciprofloxacin as compared to its literature reported rate of resistance of less than 10% to these antibiotics (Section 2.1.5. 2.1). *E. Coli,* by these results, has been seen to demonstrate higher levels of resistance to these specified antibiotics in hospitals in Lesotho than levels of resistance of the pathogen to these antibiotics as generally reported in the literature.

The 22% resistance rate of *E. coli* to ciprofloxacin which otherwise was reported together with nitrofurantoin in the literature to be less than 1%, is of concern as this is indicative of an unprecedented high resistance rate of the pathogen to ciprofloxacin. that could have been resulting in high rates of treatment failures of *E. coli* infections treated with ciprofloxacin. Under dosing of the antibiotic in treating genitourinary tract infections, for which *E. coli* among other pathogens, is an associated causative agent coupled with the extensive use of the antibiotic in treating the infections are hypothesised as possible causes of the development of resistance of *E. coli* to the ciprofloxacin. Antibiotic under-dosing or its over-use have both been paradoxically implicated as causes of resistance development of bacterial pathogens to the agents (World Health Organization, 2001:1).

Ciprofloxacin is empirically prescribed in Lesotho as part of a recommended treatment protocol for sexually transmitted diseases with urethral and vaginal discharges as symptoms. Targeted against *Neisseria gonorrhoea* it is prescribed as a single dose of 500 mg in accordance with recommendations in the standard treatment guidelines of Lesotho (Ministry of Health & Social Welfare, 2006: 65,66). Used this way, the antibiotic has a high propensity of being equally prescribed, and as same single dosage regimens, in urinary tract infections occurring concurrently with penile or vaginal discharges and for

which *E. coli* has been shown as one of its associated pathogens (Results: Section 4.1.2.5). Prescribed at a rate of 73.7% (Table 4.1.36) ciprofloxacin is most frequently prescribed for genitourinary tract infections presenting as uncomplicated urinary tract infections or urinary tract infections complicated with penile and vaginal discharges in outpatient departments. Stamm, (2005:1719) recommends a 3-day and a 7-14 day treatment regimen of the quinolones in the respective treatments of acute uncomplicated and complicated urinary tract infections diagnosed respectively as cystitis and pyelonephritis. The author noted that that single dose therapy does not eradicate vaginal colonisation with *E. coli* as effectively as do longer regimens (Stamm 2005:1718). As indicated above, incomplete eradication of *E. coli* with single doses of ciprofloxacin in genitourinary infections has the implication of promoting resistance of the pathogen to the antibiotic while its high frequency of prescription in the infections may result in resistance development by mechanisms of antibiotic selective pressure.

E. coli was also observed to show resistance rates of 14% to nitrofurantoin, a resistance rate much higher than the less than 1% rate of resistance of the pathogen to the antibiotic as reported in the literature. This could possibly be caused by mechanisms of antibiotic selective pressure for reasons of the antibiotic being prescribed for almost all cases of urinary tract infections in accordance with prevailing treatment protocols of the infection in Lesotho. Current treatment protocol of urinary tract infections in the country advocates for a syndromic approach in which nitrofurantoin or nalidixic acid is empirically prescribed as antibiotics of choice for suspected infections of the urinary tract. The approach is seen as having the disadvantage of promoting over-use of the antibiotics and it could be a cause of the observed increase in the pathogen's resistance to the antibiotic.

- ***Klebsiella* and *Proteus* spp**

With the exception of a few differences, *Klebsiella* and *Proteus* spp showed marked similarities with *Escherichia coli* in their reported sensitivities or resistances to formulary antibiotics (Table 4.2.25). Both organisms respectively exhibited high rates of resistance to ampicillin (83% and 81% in comparison with 84% for *E. coli*), co-trimoxazole (68% and 76% compared with 65% for *E. coli*), tetracycline (63 and 81% compared with 68% for *E. coli*) and chloramphenicol (47% and 52% also compared with 43% for *E. coli*). They similarly showed, as seen with *E. coli,* comparatively much lower resistances with

gentamicin (29% and 21% in comparison with 22% seen with *E. coli*), ciprofloxacin (26% and 10% in comparison with 22% for *E. coli*) and nalidixic acid (23% for either pathogen in comparison with the 19% seen with *E. coli*). Significant differences noted in the reported sensitivity patterns included the high resistance (51%) exhibited by *Klebsiella* spp to the TGCs (ceftriaxone and cefotaxime) in comparison with the low resistance rates of 9% and 12% reported for *Proteus* spp and *E. coli* to the antibiotics as well as the high resistance rates of 64% exhibited by *Proteus* spp to amikacin as again compared with the low resistance rates of 6% and 11% seen respectively with *Klebsiella* spp and *E coli*.

The similarities of the sensitivity patterns of all three enteric GNB are predictably expressions of shared class characteristics with respect to mechanisms of their development of resistance to antibiotics. As literature findings indicate, *E. coli, Klebsiella* spp and certain species of *Proteus* (*P. vulgaris* and *P. penneri*) are intrinsically resistant to the penicillins on account of their β-lactamase production capabilities. The class of bacteria also demonstrate great propensity to developing multi-resistant strains through transfer of plasmid containing genes encoding for extended-spectrum β-lactamases (ESBLs) (Sections 2.1.5.2.2 and 2.1.5.2.3).

The observed high resistance rate of *Klebsiella* spp to the TGCs conforms with literature reported increasing rates of resistance of the organisms to the TGCs mediated by plasmid containing genes for ESBLs that have been linked with resistance determinants for aminoglycosides, tetracyclines and co-trimoxazole (Russo, 2005:883). Significantly this finding has established the existence of TGC resistant strains of *Klebsiella* spp in hospital environments in Lesotho. As the literature documents, spectacular increases in resistance rates of *Klebsiella* to ceftazidime, a third generation cephalosporin, and also amikacin were seen among bacterial isolates from specimens obtained from a section of a hospital where empiric prescription of these antibiotics was done as a policy, in the treatment of *K pneumoniae* infections (Ariffin *et al.,* 1999:24). Indications were that emergence of such resistant strains of the organism were a direct result of the empiric use of the specified antibiotics (Ariffin *et al.,* 1999:24). Results of research Phase I, as reported in subsection 4.1.3 indicated as many as 98.7% (calculated; Table 4.1.2) of all antibiotic prescriptions analysed for inpatients to be empirically written, showing that TGCs, like almost all antibiotics, were prescribed empirically mostly in the patient group.

By inferences based on literature purported reasons of observed increases in resistance of *Klebsiella* spp to TGCs and amikacin, it could be stated that observed high rates of resistance of *Klebsiella* spp to TGCs in hospitals in Lesotho, is a direct result of an empiric over-use of this antibiotic in the treatment of infections.

Proteus mirabilis with the exception of tetracycline, is characteristically very susceptible to many antibiotics including β-lactam antibiotics but can through acquisition of plasmid propagated ESBL genes develop resistance towards a number of antibiotics. It is particularly reported to demonstrate multiple antibiotic resistance to a range of antibiotics including TGCs, fourth generation cephalosporins (FGCs), gentamicin, fluoroquinolones and co-trimoxazole (Luzzaro *et al.,* 2001:131). *P. vulgaris* and *P. penneri*, mostly isolated from specimens obtained from hospital or long-term care facility contracted infections, are intrinsically resistant to β-lactam antibiotics and exhibit multi-drug resistances to many antibiotics.

Antibiotic sensitivity patterns reported for *Proteus* spp isolates from study site hospitals indicated profound resistance of the organisms to the β-lactam antibiotics and amikacin but showed comparatively high sensitivities to gentamicin, ciprofloxacin and the TGCs (ceftriaxone and cefotaxime) (Table 4.2.5). These sensitivity patterns are more characteristic of *P. vulgaris* or *P. penneri* than of *P. mirabilis* strains which, though they can demonstrate acquired resistance towards β-lactam antibiotics through ESBL mediated resistance mechanisms as indicated, are generally noted to be intrinsically susceptible to the β-lactam and many other antibiotics. Based on these it could be inferred that *Proteus* species isolated by laboratories are composed mostly of *P. vulgaris* and *P penneri* from hospital environments and not community associated *P. mirabilis* strains. By this inference, antibiotic selections for infections in which *Proteus* spp are implicated as causative agents should essentially target *P. vulgaris* or *P. penneri* rather than *P. mirabilis* except if such infections are coming from the community, in which case *P. mirabilis* would be the more probable assaulting pathogens. Such infections according to study results include ear, skin and soft tissue and urinary tract infections, bacteraemia, and primary or spontaneous bacterial peritonitis.

The observed low activity of co-trimoxazole to *Proteus* spp, which presumably are composed mainly of *P. vulgaris* and *P. penneri* based on interpretations of study results, is of concern as it puts into doubt the extent of treatment successes achieved with the

use of the antibacterial agent in treating infections for which it is prescribed. This expression of doubts of about the extent of treatment successes achieved with co-trimoxazole is made considering further that most other bacterial isolates by results of the study demonstrate equally high resistances towards it and that it is one of the most used agents in treating infections at study site hospitals. Co-trimoxazole is prescribed at frequency rates of 10.8%, fourth to ampicillin, cloxacillin and metronidazole in inpatient departments and 17%, second to ampicillin in outpatient departments (Tables 4.1.15 and 4.1.33). These frequency rates of prescribing as already indicated, make the antibacterial agent one of the most empirically prescribed antibacterial agents in the treatment of most infections at study site hospitals. The agent, as also in the cases of the aminoglycosides, quinolones, imipenem and the FGCs, is reported in the literature to demonstrate excellent activity towards *Proteus* spp (Section 2.1.5.2.3) contrary to the high rate of resistance of 76% seen to be exhibited by the isolates towards it. Considering the high rate prescribing of co-trimoxazole at study site hospitals, the most probable mechanism by which these reported resistances appeared to have been developed, is postulated to be due to selective pressure exerted by an over-use of the antibiotic (Colgan & Powers, 2001:999). The postulate does not, however, discount contributions by other mechanisms in the development of resistance of *Proteus* spp and other pathogens to co-trimoxazole.

Studies have shown that withdrawing an antibiotic against which pathogens have developed resistance from regular use for given time periods or reducing the rates of use of such antibiotics do reverse the clinical problems of resistance to such antibiotics. Typical such studies were reported by Gould (1999:460) and included as examples the demonstration of rapid reversal of major clinical problems of resistance to chloramphenicol, erythromycin and tetracycline in *S. aureus* on withdrawal of these antibiotics from clinical use; the control of an outbreak of multi-resistant Klebsiella infection following a necessary cessation of all antibiotic prescribing on a neurosurgical intensive care unit and the successful control in the UK of an outbreak of gentamicin resistant *Pseudomonas aeruginosa* on a burns unit when a ban on topical gentamicin was put in place. In line with results of these studies as the literature reports, it is recommended that co-trimoxazole is withdrawn from clinical use for some time period or the rate of its prescription at study site hospitals greatly curtailed to reverse the clinical problems of resistance associated with the use of the antibiotic at study site hospitals.

Currently important anti-pseudomonal antibiotics are considered to include the aminoglycosides, broad spectrum penicillins (e.g. piperacillin), third generation cephalosporins (e.g. ceftazidime) and the quinolones (e.g. ciprofloxacin) (Elliot et al., 2004:68)

- ***Pseudomonas spp***

According to information gathered from the literature as noted in Section 2.1.5.2.7: antibiotic sensitivity patterns of *Pseudomonas* spp vary significantly with localities and types of antibiotic use associated with them. Generally, they exhibit resistance to many antibiotics as a result of their possession of both intrinsic and acquired antibiotic resistance characteristics as well as their profound ability to form biofilms which enable them to resist antibiotic killing (Abdi-Ali *et al.*, 2005:196). Antibiotics the organisms are currently known to demonstrate appreciable degrees of sensitivities towards include the aminoglycosides, the carbapenems, the anti-pseudomonal penicillins, the cephalosporins, (TGCs and FGCs) and the quinolones (Elliot et al., 2004:68). According to one study, (Blandino *et al.*, 2004:516) most activities in the ranges of between 72% - 79.6% were demonstrated by the aminoglycosides, the carbapenems and the broad spectrum penicillins against the organisms, with amikacin among these groups of antibiotics showing the highest activity. The third (ceftazidime) and fourth (cefepime) generation cephalosporins and ciprofloxacin were similarly shown to exhibit much lower levels of activity that ranged from between 45.4% for ciprofloxacin to 64.5% for TGC (ceftazidime). In localities where there is rampant use of some of these antibiotics the organisms were found to demonstrate high degrees of resistance to some of them to which they are known to be sensitive. In comparison to a reported highest activity of almost 80% shown by amikacin at a study site, amikacin for example was seen to exhibit only up to 49% activity against the organisms at a Burn centre locality where the antibiotic was much used (Lari *et al.,* 1998:637).

Pseudomonas antibiotic sensitivity patterns, as study results showed, can be said to be in line with predictions from literature findings as recapped above. They are also similar to those of the enteric GNB studied, with respect to their demonstration of appreciable sensitivities to the aminoglycosides (gentamicin and amikacin), the quinolones (ciprofloxacin and nalidixic acid) and the TGCs (ceftriaxone and cefotaxime) and profound resistance to ampicillin, co-trimoxazole, tetracycline and chloramphenicol.

Unlike *E. coli* and *Klebsiella,* and worse than *Proteus* spp, the organisms rather demonstrated high rates of resistance to nitrofurantoin. Their exhibition of very high sensitivities to the aminoglycosides (gentamicin 92% and amikacin 94%) and the fluoroquinolones (ciprofloxacin 90%) are particularly significant in view of current problems of pseudomonas antibiotic resistance as reported in the literature.

Amikacin by results of research Phase I, is rarely used as a regular antibiotic in empiric treatment of infections and the preservation of the high activity of the antibiotic against *Pseudomonas* as the study results had shown, can be most reasonably attributed to this rare use of the antibiotic at study sites. This is speculated from explanations given by Lari *et al.,* (1998:637) as reported in Section 2.1.5.2.7, to explain a 49% resistance rate demonstrated by *Pseudomonas* species to amikacin at a burn centre where amikacin and other antibiotics were much used. The researchers attributed the development of resistance of *Pseudomonas* to amikacin to mechanisms that they believed involved selection of strains of the organism resistant to the antibiotic for reasons of it being over-used. In clinical environments where amikacin is not much used as seen in the case of study site hospitals for this study, possibilities are that there would be no such antibiotic over-use selective pressures to cause resistance development of the organism to the antibiotic. Gentamicin, the preferred aminoglycoside in the treatment of GNB infections as again shown by results of research Phase I (Sections 4.1.1.5), have also been seen to demonstrate high activity against the organisms in spite of its very frequent prescription in the treatment of these infections. The reason for this high activity of the antibiotic against pseudomonas cannot be easily explained. From the results of these sensitivity determinations, however, the aminoglycoside antibiotics can be considered as the most useful anti-pseudomonal antibiotics in Lesotho's antibiotic armoury and may remain so for a long time if used judiciously. As indicated by Elliot (2004:68) and Ohl & Pollack (2005:890-893) *Pseudomonas* are very important opportunistic human pathogens that cause infections in patients in whom the immune system is compromised as in HIV and AIDS. With current rates in HIV prevalence of 24% among the Basotho population as mentioned in earlier paragraphs, possible trends towards pseudomonas infections could be expected to in the population to warrant an increase and hence an over-use of these anti-pseudomonal antibiotics. Like the aminoglycosides, the quinolones (ciprofloxacin and nalidixic acid) and the TGCs (cefotaxime and ceftriaxone) also have good prospects of continuous use as effective anti-pseudomonal antibiotics.

Literature reports of the demonstrations of rather moderate levels of activities of these antibiotics against the pathogens (Blandino *et al.*, 2004:516) rather show that their resistances to pseudomonas antibiotic resistance mechanisms are not as effective as those of the aminoglycosides. They might not be depended on for a longer time to come as effective anti-pseudomonal drugs in the future in the event of their increased use in parallel to that of increasing rates of pseudomonal infections resulting from increasing rates of HIV infection in the population. For purposes of maintaining the effectiveness of currently used anti-pseudomonal antibiotics at the levels shown by results of this study, it is recommended that prescribers prescribe these antibiotics judiciously by adhering to principles of antibiotic prescribing and basing their judgements on which antibiotic to prescribe on results of culture sensitivity tests.

- **Other gram-negative bacteria**

Analysis of culture sensitivity data gathered on the majority of gram-negative bacteria randomly isolated, cultured and tested against few antibiotics, provided too limited information on their antibiotic sensitivity patterns for use in selecting antibiotics for the empiric treatment of infections caused by them. For all such organisms, as results have indicated, it is necessary to base antibiotic treatment of their infections on results of culture sensitivity tests. Using such limited information as curtain raisers on what could be the true sensitivity patterns for some of these organisms that were tested for a few more times than the others however, some realistic predictions can be made on sensitivity patterns of these organisms to guide in the antibiotic selections for their infections. *Neisseria spp* and *Haemophilus influenzae* are discussed for this purpose.

- ***Neisseria spp***

A review of the literature (Section 2.1.5.1.1) noted a remarkable ability of *N. gonorrhoea* to develop resistance to various antibiotics including β-lactam antibiotics, the quinolones and tetracyclines through acquisition of plasmid containing genes for ESBLs or chromosomal mutations to result in resistance to specific antibiotics (Inglis, 2003:253). Stathi *et al.* (2007:S306). Antibiotic susceptibility of reports on *N. gonorrhoea* by some studies noted resistances of the organisms to the levels of 98% for penicillin, 95% for tetracycline 74% for co-trimoxazole and 55% for erythromycin. Same or similar reports indicated resistances of 11.3% - 33.3% of the pathogen to the fluoroquinolones, norfloxacin and ciprofloxacin, and 15% to gentamicin (Zachariah *et al.*, 2002:234).

Neisseria meningitidis, though, have been noticed to also produce acquired resistance through β - lactamase production yet to be associated with a high degree of penicillin resistance. *Neisseria meningitidis* resistance to penicillin is considered to be rather uncommon (Inglis, 2003:253) and there are no reports of resistance of the pathogens to the extended-spectrum cephalosporins e.g. cefotaxime and ceftriaxone which are most frequently used as antibiotics for the treatment of invasive meningococcal disease in developed (Tzanakaki & Mastrantonio, 2006:621).

Reports of antibiotic sensitivity patterns of *Neisseria* spp in the literature, as summarised above, showed both *N. gonorrhoea* and *N. meningitidis* to demonstrate different patterns of sensitivities to antibiotics with *N. gonorrhoea* reportedly demonstrating higher propensity to developing resistance to commonly used antibiotics than *N. meningitidis* (Inglis, 2003:253; Zachariah *et al.*, 2002:234; Tzanakaki & Mastrantonio, 2006:621). The reporting by study site laboratories of results of culture sensitivity tests as characteristics for the species and not for the individual pathogens within the group limits interpretations of the reported culture sensitivity test results to reflect which of the two pathogens showed the reported sensitivities to given antibiotics. The handicap is particularly real when it is considered that isolates of the species tested for their sensitivities were obtained in almost equal proportions from cerebrospinal fluid and vaginal swab specimens (Table 4.2.2), the two specimen sources from which *N. meningitidis* and *N. gonorrhoea* are more likely to be isolated because of their respective associations with meningitis and gonorrhoea as causative agents. In the light of this limitation sensitivities determined for the species from culture sensitivity test results as reported by laboratories cannot be interpreted to show patterns of sensitivities of the respective pathogens to currently used antibiotics for their meaningful selection in treating meningitis and gonorrhoea.

- ***Haemophilus influenzae* (*H. Influenzae*)**

The acceptability of determined rates of sensitivities or resistances of *Haemophilus influenzae* is highly compromised by the small sample size of analysed data. By interpreting these results in the light of literature reported antibiotic sensitivity patterns of the pathogen, however, one can to some extent to predict local antibiotic sensitivity patterns of the organism that could usefully guide in the empiric antibiotic treatment of *H. influenzae* infections.

Haemophilus influenzae by literature notations (Section 2.1.5.2.6) is reported to be highly susceptible to major antibiotics against which they were tested in a number of studies. These include reports of such high sensitivity rates 96.3% to 100% to a number of antibiotics including TGCs, ciprofloxacin and azithromycin to which they showed 100% sensitivity, amoxicillin/clavulanic (99.9%), chloramphenicol (98.8%) and tetracycline 96.3% (Marchese *et al.,* 2005:10). Some study reports generalised the organism's resistance rates to be as low as 7.5%, 10.7 and 9.4 % respectively for chloramphenicol, tetracycline and co-trimoxazole but in countries with high β-lactamase producing *H. influenzae*, resistance rates of the organisms to these antibiotics were respectively seen to be as high as 29.4%, 33.3% and 41.2% (Inoue *et al.*, 2004:47). This finding links the development of resistance of *H. influenzae* to these antibiotics to their ability to produce β-lactamase.

H. influenzae was found to be 50% resistant to ampicillin by this study, a resistance rate suggestive of about 50% of strains of the organisms tested being β-lactamase producing. The literature reports about 25% of strains of the organism being β-lactamase producing (Murphy, 2005:865; Elliot *et al.*, 2004:59). Despite limitations posed by unacceptably low numbers of isolates of the organism tested, the reported low sensitivity of the organism to ampicillin points to the possibility of a high prevalence of β-lactamase producing strains within the population. The 100% reported resistance of co-trimoxazole, though, may also not be accepted as reflecting the true sensitivity rate of the organism to the antibiotic for the same reasons could be taken in the least as an indication of possible high prevalence rate of co-trimoxazole resistant *H. influenzae* among the population. This may be so particularly in this situation where a high utilisation rate of the antibiotic among the population as established by results of research Phase I (Sections 4.1.1.4 & 4.1.2.5) can orchestrate the development of resistance of the organisms to the antibiotic. Tetracycline, chloramphenicol and gentamicin were reported to demonstrate 100% activity against the organism. Compared to literature reported sensitivity patterns of *H. influenzae* to these antibiotics as reported above, these could be accepted as true sensitivities of *H. influenzae* to the antibiotics despite the small numbers of the organisms tested. Both tetracycline and chloramphenicol by results of research Phase I (Section 4.1.1.4 & 4.1.2.5) are not much used antibiotics and are most likely to have their activities against most pathogens preserved. Activities of the aminoglycosides (gentamicin and amikacin) against *H. influenzae* have not been reported in the literature

for comparison with the 100% sensitivity seen to be shown by the organism towards this antibiotic. Like other antibiotics, for example, ciprofloxacin and TGCs that characteristically exhibit high activities against GNB and which have been reported in the literature to demonstrate high activities towards the organism (Marchese *et al.,* 2005:10), gentamicin by its reported activity against *H. influenzae* is assumed to have a preserved high activity against the organism despite its high usage pattern as shown by results of research Phase I Sections 4.1.1.4 and 4.1.2.5.

Neisseria spp and *Haemophilus influenzae* are important aetiological agents associated with serious infections for which antibiotics are empirically prescribed. There is a lack of precise information on their sensitivity patterns to antibiotics commonly used in Lesotho compromise and on prescribers' abilities to select the most effective antibiotics in the empiric treatment of their infections. This study could not provide this information due to limitations posed by unavailability of sufficient data for analysis. It is recommended that more culture sensitivity testing of these organisms be done in future at study hospitals to provide the data needed for analysis to provide this information. For the same reasons, it is similarly recommended that more culture sensitivity testing to be done on other isolates of gram-negative bacteria, namely, *Acinetobacter*, *Enterobacter*, *Peptococcus*, *Bacteroides*, *Shigella* and *Salmonella* species, to provide data needed for determining local antibiotic sensitivity patterns for this group of pathogens. Culture sensitivity data currently available for these organisms are either too scanty or completely unavailable for such determinations.

4.2.3.2 Variations in percentage yearly resistances of bacterial isolates to formulary antibiotics

The section presents results of analysis of culture sensitivity test results data from January 2000 to December 2005 to establish patterns of variations in yearly percentage resistances of bacterial isolates to formulary antibiotics.

Percentage resistances determined for organisms in the year 2000 were taken as pathogens' baseline resistance values and considered against values determined for subsequent years to determine whether there had been increases or decreases over the baseline percentage resistance values of the organism for the year 2000. Plots of yearly resistances of pathogens to a given antibiotic against years for which data had been

collected produced trends in pathogens' resistances to the antibiotic over the specified years to show increasing or decreasing trends in resistances of pathogens to the given antibiotic over the years for which data had been collected.

Reported frequencies of culture sensitivity testing of certain bacterial isolates against given antibiotics in certain years were found to be very low [generally below ten (10)] in comparison with similar frequencies of testing the isolates in other years against the antibiotic in question. Calculated percentage resistances of the organisms in those years of low frequencies of testing were found generally to be out of range of their percentage resistances in years in which they were tested at higher frequencies for their sensitivities against the antibiotic, producing trends in yearly resistance variations that cannot be reasonably interpreted. In such situations it was found necessary to disregard such percentage resistance determinations in the reporting of results for reasons of producing variations in yearly percentage resistances that could be interpreted as increasing, decreasing or remaining the same over the data collection period.

4.2.3.2.1 Results

Percentage yearly resistances of bacterial isolates to given antibiotics are shown in Tables 4.2.6 to 4.2.18. Yearly variations in pathogens' resistances to given antibiotics as well as calculated increases or decreases in organisms' year 2000 resistance rates to given antibiotics over 2001 to the 2005 year period that followed are graphically presented in Figures 4.2.17(a) and (b) through 4.2.29(a) and (b).

Variations in organisms' yearly determined percentage resistances as well as increases or decreases in their average yearly percentage resistances in the period 2001 to 2005 over or below their resistances in year 2000 for respective antibiotics as noted from tables and figures are as outlined below:

- **Ampicillin**

From results presentations in Table 4.2.6 and Figures 4.2.12 (a) and (b) the following have been noted as variations in resistances of pathogens to ampicillin from 2000 to 2005.

Gram-negative bacilli (GNB)

- Yearly resistance rates of gram-negative bacilli to ampicillin generally remained high and stable over the six-year period for which bacterial pathogen sensitivity data were studied.

- *Escherichia coli* and *Klebsiella* spp significantly demonstrated high yearly resistance rates of between 75% and 89% that remained stable with little variation within the six-year period of study.
- *Proteus* spp showed progressive increases in its yearly percentage resistance to ampicillin from a reported 58% in 2000 to a maximum 81% in 2003 from where it remained stable.
- *Pseudomonas* spp demonstrated a stable high resistance to ampicillin in the range of 89 and 93% within the six-year period for which data were collected and analysed. One exception of a comparatively low percentage resistance of 60% was reported for the year 2004
- Average yearly resistance rates of all four GNB to ampicillin from 2001 to 2005 showed increases of 9.0%, 11.2% and 11.2% for *Escherichia coli, Klebsiella* and *Proteus* spp respectively and a decrease of 13.4% for *Pseudomonas* spp higher than and below their year 2000 yearly resistance rates.

Gram-positive bacilli

- *Staphylococcus aureus* in general demonstrated progressive increases in its yearly resistance to ampicillin from a 47% resistance rate in year 2000 to maximum levels of between 68% and 71% in years 2003, 2004 and 2005.
- *Streptococcus pneumoniae* (α-haemolytic streptococci) maintained a stable low percentage yearly resistance in the range of 0.0% and 13.0% to ampicillin within the six-year study period. In the exception of a reported 0.0% percentage yearly resistance in year 2001, percentage yearly resistances of the organism to ampicillin varied between 8% and 13% within the 2000 to 2005 period for which data were studied.
- *Streptococcus pyogenes* (β-haemolytic streptococci) exhibited percentage yearly resistances to ampicillin that varied between 14% and 36% during the 2000 to 2005 period for which data were studied with a yearly variation trend that showed an over all increase in resistance by year 2005.
- Non-haemolytic streptococci (enterococci) showed percentage yearly resistances to the antibiotic that decreased from a high 42% in year 2000 to a low 16% in year 2005.

Table 4.2.6 Yearly percentage pathogen resistances to **AMPICILLIN** from Jan 2000 to Dec 2005

Pathogen	Frequencies of pathogen sensitivity testing against antibiotics and calculated percentage resistances and increase in resistances																	
	Jan to Dec 2000			Jan to Dec 2001			Jan to Dec 2002			Jan to Dec 2003			Jan to Dec 2004			Jan to Dec 2005		
	T	R	%R	T	R	%R	T	R	%R	T	R	%R	T	R	%R	T	R	%R
α- Haemolytic strep(*S. pneumonia*)	20	2	10	24	0	0	13	1	8	16	2	13	24	2	8	15	2	13
β-Haemolytic strep (*S. pyogenes*)	21	3	14	22	4	18	6	2	33	28	10	36	20	5	25	15	3	20
Non Haemolytic streptococci (Enterococci spp)	12	5	46	38	7	22	22	10	45	5	1	20	25	6	24	14	2	16
Staphylococcus aureus	232	110	47	209	128	61	82	42	51	253	172	68	219	155	71	226	155	69
Escherichia coli	248	217	76	447	377	84	265	226	85	248	206	83	217	193	89	153	128	84
Klebsiella spp	79	59	75	134	122	91	45	39	87	96	84	88	70	60	86	33	26	79
Pseudomonas spp	14	13	93	22	18	82	19	17	89	106	83	78	15	9	60	9	8	89
Proteus spp	74	43	58	86	49	57	36	23	63.9	27	22	81	95	70	74	67	53	79

Table 4.2.7 Yearly percentage pathogen resistances to **PENICILLIN** from Jan 2000 to Dec 2005

Pathogen	Frequencies of pathogen sensitivity testing against antibiotics and calculated percentage resistances and increase in resistances																	
	Jan to Dec 2000			Jan to Dec 2001			Jan to Dec 2002			Jan to Dec 2003			Jan to Dec 2004			Jan to Dec 2005		
	T	R	%R	T	R	%R	T	R	%R	T	R	%R	T	R	%R	T	R	%R
α- Haemolytic strep (*S. pneumoniae*)	20	4	20	17	2	12	10	2	20	19	5	26.3	22	4	18.2	13	4	30.8
β-Haemolytic strep (*S. pyogenes*)	19	5	26.3	18	8	44.4	6	4	66.7	10	4	40	18	9	50	14	3	21.4
Non Haemolytic strep (Enterococci)	6	6	100	27	10	37	14	9	64.3	17	9	52.9	20	9	45	15	6	40
Staphylococcus aureus	206	142	68.9	197	143	72.6	74	48	64.9	171	149	87.1	159	125	78.6	183	157	85.8
Escherichia coli	15	12	80	19	16	84.2	8	8	100	7	4	57	4	3	75	3	1	33.3
Klebsiella spp	7	7	100	6	6	100	2	2	100	4	3	75	1	0	0	2	2	100
Proteus spp	2	1	50	6	2	33.3	4	4	100	4	3	75	3	2	66.7	3	3	100

ABREVIATIONS: T: Total number of pathogens tested in year; R: Number of pathogens resistant; %R: Yearly percentage resistance or yearly rate of resistance

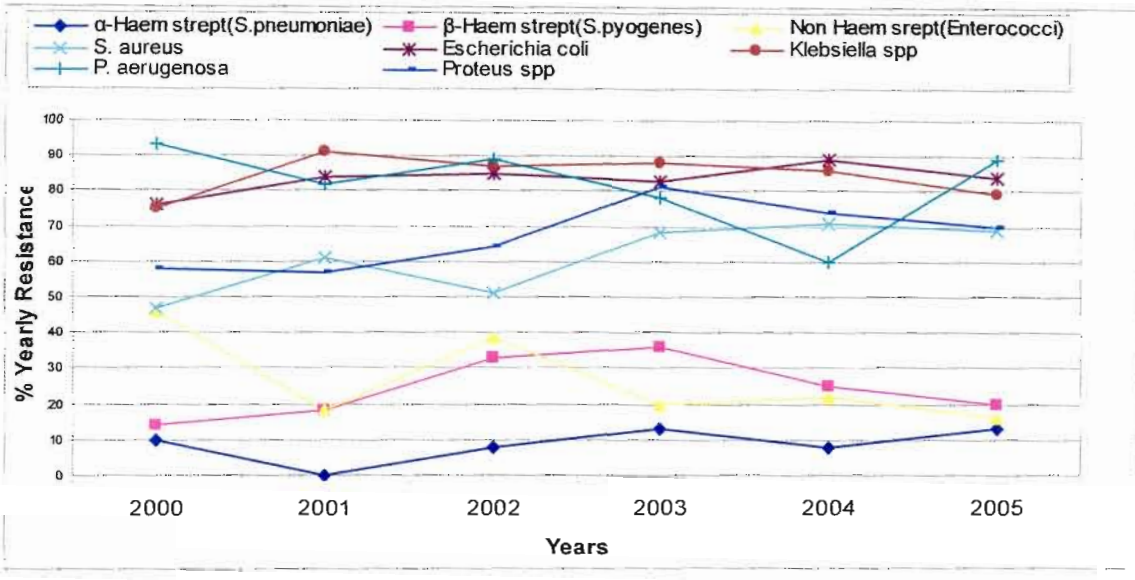

Fig. 4.2.18 (a) Yearly variations in percentage pathogen resistances to **Ampicillin** from year 2000 to 2005

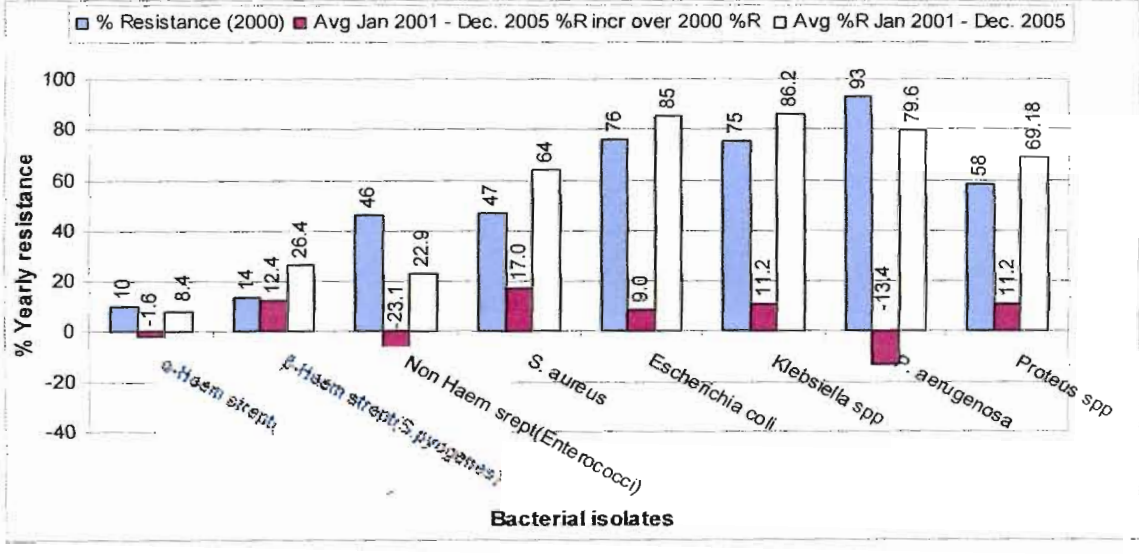

Fig. 4.2.18(b) Pathogen yearly resistances to **Ampicillin** showing increases or decreases of pathogens' average resistance rates in 2001-2005 higher than or below their 2000 resistance rates

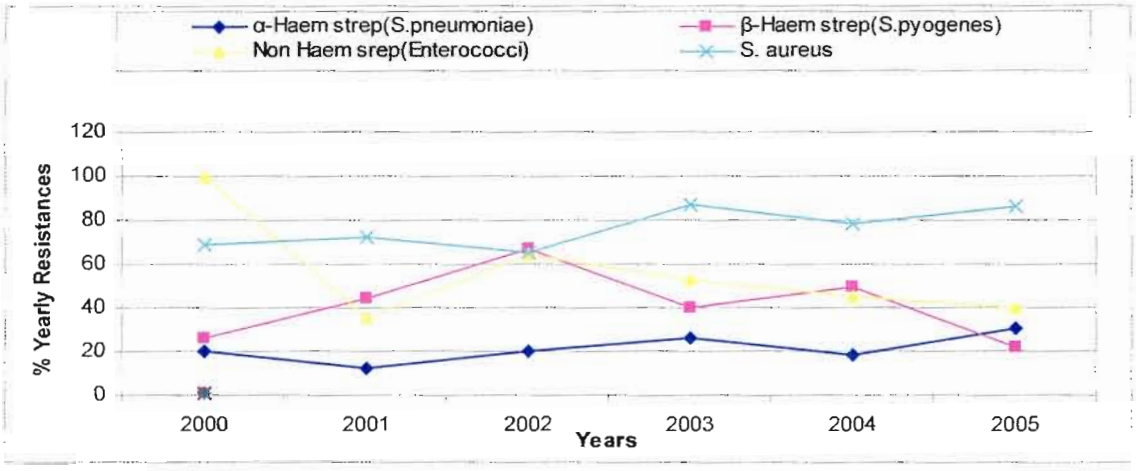

Fig. 4.2.19(a) Yearly variations in percentage pathogen resistances to **Penicillin** from year 2000 to 2005

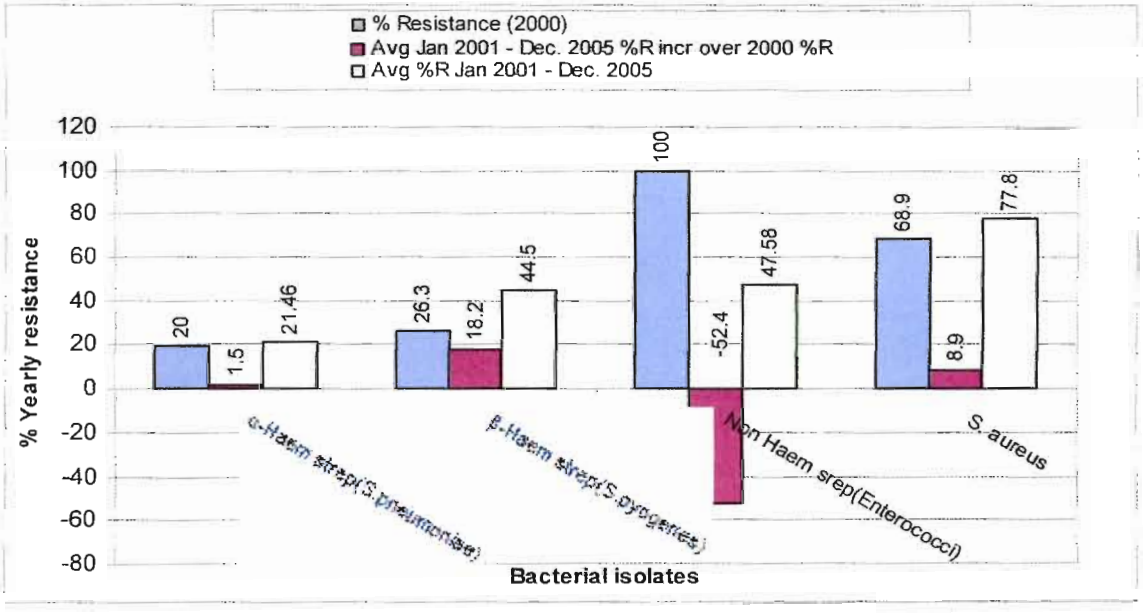

Fig 4.2.19(b) Pathogen yearly resistances to **Penicillin** showing increases or decreases of pathogens' average resistance rates in 2001-2005 higher than or below their 2000 resistance rates

- *Staphylococcus aureus* and β-haemolytic streptococci (*S. pyogenes*) showed increases of 17.0% and 12.4% respectively while α-haemolytic streptococci (*Streptococcus pneumoniae*) and Non-haemolytic streptococci (enterococci and non-enterococcal streptococci) respectively demonstrated 1.6% and 23.1% decreases in the same average yearly percentage resistances higher than and below their percentage yearly resistances in year 2000.

♦ **Penicillin**

Figure 4.2.18(a) shows trends in variations in organisms' yearly resistance rates to penicillin within the 2000 to 2005 period of culture sensitivity test results data studied and presented in Figure 4.2.18 (b), increases or decreases in average resistance rates of organisms within 2001 to 2005 higher than or below their percentage yearly resistances in 2000.

Gram-positive cocci

Staphylococcus aureus generally showed progressive increases in its yearly resistance to penicillin from a 68.9% resistance rate in year 2000 to a maximum rate of 87.1% in 2003 which remained stable through 2004 and 2005.

- *Streptococcus pneumoniae* (α-haemolytic streptococci), demonstrated a stable resistance rate to penicillin that varied between 12.0% and 30.8% within the study period.
- Yearly resistance rates of *Streptococcus pyogenes* (β-haemolytic streptococci) to the antibiotic increased from 26.3% in 2000 to 64.9% in 2002 and then decreased progressively to a low 21.4% in 2005.
- Non-haemolytic streptococci (enterococci and non-enterococcal streptococci) showed a trend in yearly resistance rates to penicillin that decreased from a high 100% in 2000 to a low 40% in 2005.
- *Staphylococcus aureus, Streptococcus pneumoniae* and *S. pyogenes* showed 8.8%, 1.6% and 18.2% increases respectively in their average resistance rates between 2001 and 2005 higher than their percentage yearly resistances to the antibiotic in year 2000. Non-haemolytic streptococci (enterococci and non-enterococcal streptococci) on the other hand demonstrated a 52.4% decrease in their average yearly resistance rates to penicillin within years 2001 to 2005 below their year 2000 resistance rates.

- **Erythromycin**

Variations in percentage yearly resistances of bacterial isolates to erythromycin from 2000 to 2005 are shown in Figure 4.2.19 (a). Figure 4.2.19 (b) similarly shows increases or decreases in average percentage yearly resistances of organisms in the period 2001 to 2005 higher than or below their resistances in year 2000.

Gram-negative bacilli

- *Escherichia coli* the major organism tested against erythromycin among the GNB escalated on the average progressive increase in its resistance to the erythromycin from a 51% yearly resistance rate in 2000 to a high rate of 86% in 2005.
- The pathogen showed an increase of 18.2% in its average percentage yearly resistances to erythromycin within 2001 to 2005 period higher than its year 2000 percentage yearly resistance to the antibiotic.

Gram-positive cocci

- *Staphylococcus aureus* exhibited yearly resistance rates to erythromycin that varied between 30% and 61%, showing a trend in yearly variation which remained generally stable in the range of between 50% and 61% over the specified period of data studied. This is with the exception of an isolated low yearly resistance rate of 30% reported in 2004.
- *Streptococcus pneumoniae* (α-haemolytic streptococci) on average displayed a gradual increase in their resistance to erythromycin over the six-year period, showing a resistance rate pattern that varied between 17% and 36% without much yearly fluctuation, except for a 0.0% resistance rate noted in 2004.
- *Streptococcus pyogenes* (β-haemolytic streptococci) rather displayed an erratic trend in variations of their resistance rates to erythromycin over the 2000 to 2005 study period.
- Non-haemolytic streptococci (enterococci and non enterococcal streptococci), displayed a resistance rate pattern to erythromycin that showed a decrease following an initial high rate of 71% in year 2000 to stable and comparatively low resistance rates of between 30% and 35% in the five years (2001 to 2005) that followed.

Table 4.2.8 Yearly percentage pathogen resistances to ERYTHROMYCIN from Jan 2000 to Dec 2005

Pathogen	Frequencies of pathogen sensitivity testing against antibiotics and calculated percentage resistances and increase in resistances																	
	Jan to Dec 2000			Jan to Dec 2001			Jan to Dec 2002			Jan to Dec 2003			Jan to Dec 2004			Jan to Dec 2005		
	T	R	%R	T	R	%R	T	R	%R	T	R	%R	T	R	%R	T	R	%R
α - Haemolytic strep(S.pneumoniae, Viridans strep	13	3	23	18	3	17	10	2	20	19	5	26	13	0	0	22	8	36
β-Haemolytic strep (S. pyogenes)	18	4	22	17	8	47	5	2	40	13	2	15	13	8	61	14	1	7
Non-haemolytic strep (Enterococci spp)	6	4	67	23	8	35	15	6	40	17	6	35	20	7	35	10	3	30
S. aureus	220	126	57	153	78	51	51	31	61	180	91	51	154	46	30	266	135	51
Escherichia coli	39	20	51	6	3	50	11	9	82	7	4	57	7	5	71	14	12	86
Klebsiella spp	8	5	63	5	5	100	2	1	50	3	3	100	4	3	75	8	8	100
Pseudomonas spp	1	1	100	1	1	100	1	1	100	1	1	100	3	3	100	2	1	50
Proteus spp	4	4	100	4	4	100	1	1	100	8	6	75	5	5	100	3	3	100

Table 4.2.9 Yearly percentage pathogen resistances to METHICILLIN/CLOXACILLIN from Jan 2000 to Dec 2005-.

Pathogen	Frequencies of pathogen sensitivity testing against antibiotics and calculated percentage resistances and increase in resistances																	
	Jan to Dec 2000			Jan to Dec 2001			Jan to Dec 2002			Jan to Dec 2003			Jan to Dec 2004			Jan to Dec 2005		
	T	R	%R	T	R	%R	T	R	%R	T	R	%R	T	R	%R	T	R	%R
S. aureus	55	20	36.4	64	11	17.1	13	10	78	80	31	39	55	16	29	85	26	30.6

ABREVIATIONS: T: Total number of pathogens tested in year; R: Number of pathogens resistant; %R: Yearly percentage resistance or yearly rate of resistance

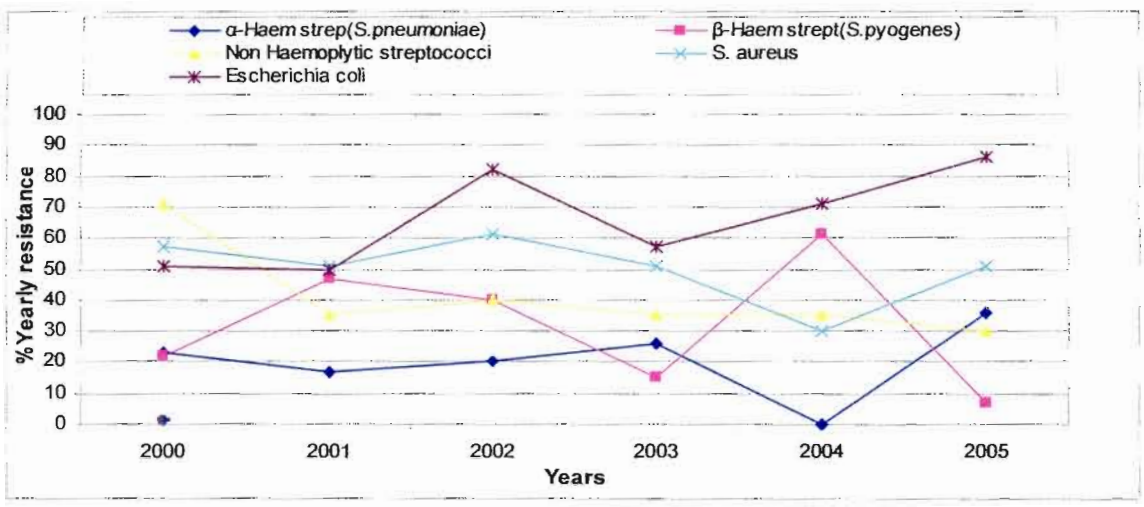

Fig 4.2.20(a) Yearly variations in percentage pathogen resistances to **Erythromycin** from year 2000 to 2005

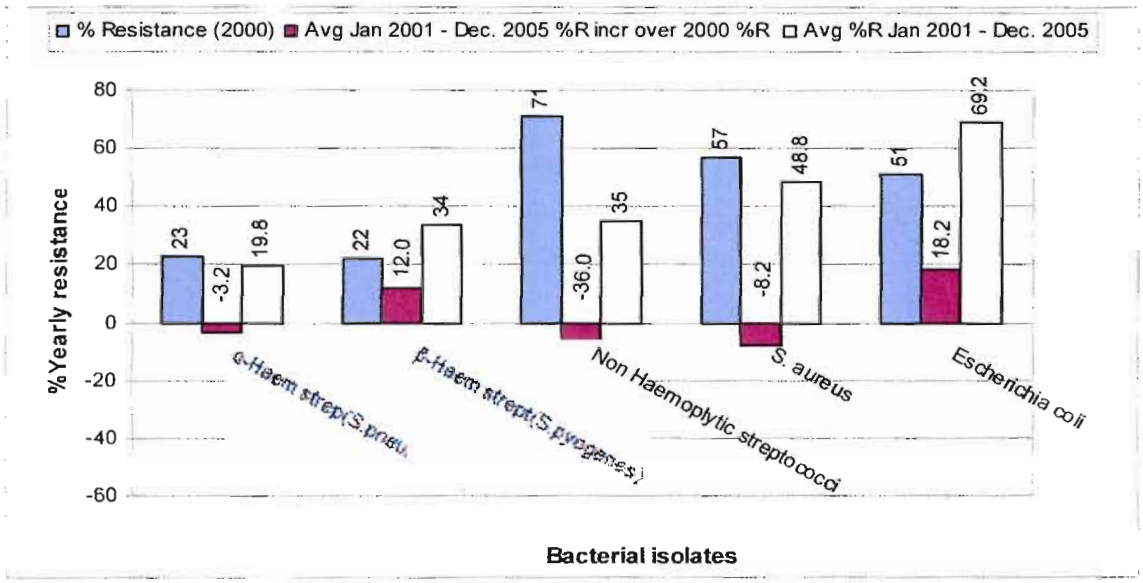

Fig 4.2.20(b) Pathogen yearly resistances to **Erythromycin** showing increases or decreases of pathogens' average resistance rates in 2001-2005 higher than or below their 2000 resistance rates

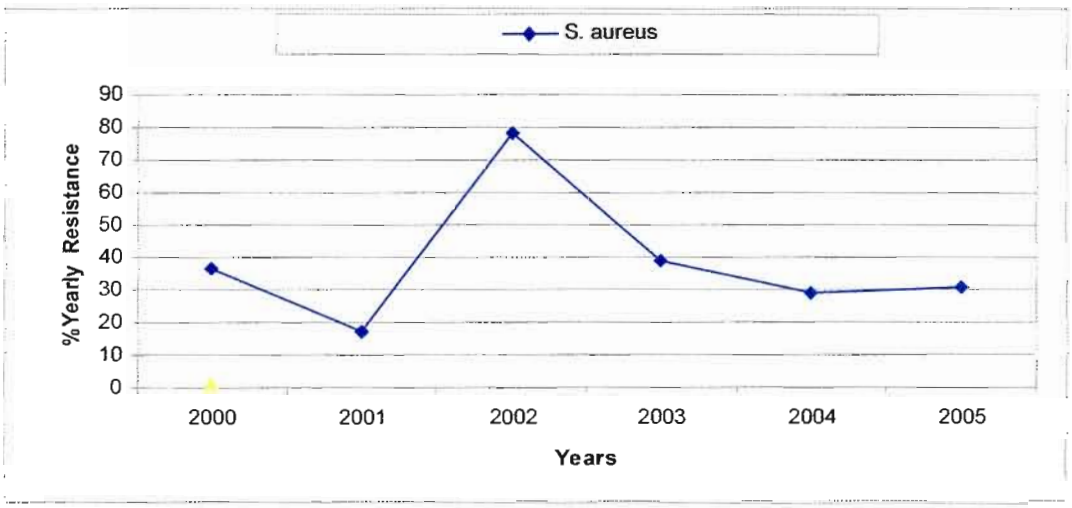

Fig 4.2.21(a) Yearly variations in percentage pathogen resistances to **Methicillin/Cloxacillin** from year 2000 to 2005

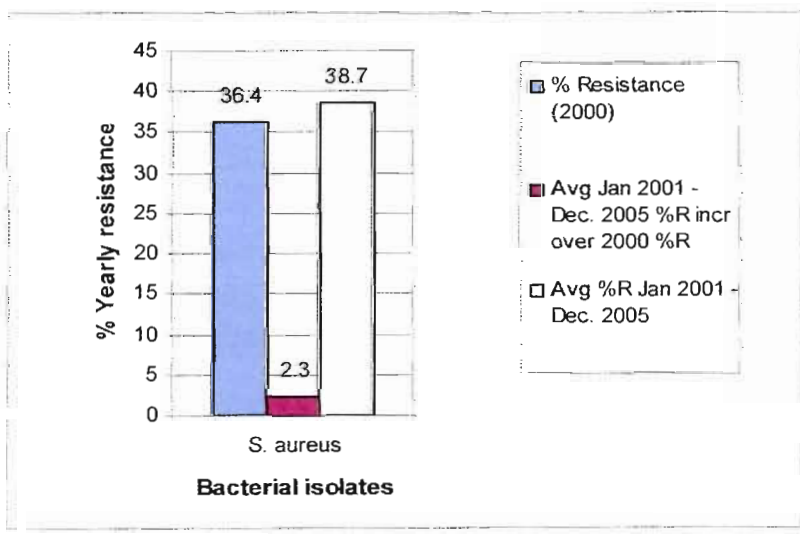

Fig 4.2.21 (b) *Staphylococcus aureus* percentage yearly resistances to **Methicillin/Cloxacillin** showing increases of pathogen's average resistance rate in 2001-2005 higher than its 2000 resistance rates

- *Staphylococcus aureus* and *S. pyogenes* respectively showed increases of 8.2% and 12.2% in their average percentage yearly resistances to erythromycin within the 2001 to 2005 period higher than their year 2000 percentage yearly resistances. *Streptococcus pneumoniae* and non-haemolytic streptococci on the other hand showed respective decreases of 3.2% and 36.0% in their average percentage yearly resistances to erythromycin within the 2001 to 2005 period below their year 2000 percentage yearly resistances to the antibiotic.

- **Methicillin/ Cloxacillin**

Methicillin was tested mainly against *Staphylococcus aureus*. Figures 4.2.20(a) and 4.2.20(b) respectively show percentage yearly resistance variations of the organism to the antibiotic over the 2000 - 2005 period for which data were collected and studied and average percentage increases in yearly resistance rates of the organism to the antibiotic within the 2001 to 2005 period higher than its year 2000 percentage yearly resistance rates.

- *Staphylococcus aureus* demonstrated percentage yearly resistance to the methicillin/cloxacillin that varied between 17.1% and 36.4%, producing a trend that showed stability in percentage yearly resistance of the pathogen to the antibiotic. This is assumed to be true if 2002 percentage resistance of 78% is ignored as an out of range data due to low frequency testing of the pathogen against the antibiotic that year.
- Average yearly resistance rates of *Staphylococcus aureus* to methicillin/cloxacillin for the period 2001 to 2005 showed a low increase of 2.3% over the pathogen's resistance rate in 2000, indicating again some degree of stability on the whole in *Staphylococcus aureus* resistance to methicillin/cloxacillin.

- **Tetracycline**

Figures 4.2.21 (a) and 4.2.21 (b) respectively show variations in bacterial isolates' yearly resistance rates to tetracycline from 2000 to 2005 and increases or decreases in average resistance rates of organisms in the period 2001 to 2005 higher than or below their resistances in year 2000. As the figures depict the following are outlined as notations on variations in percentage yearly resistance trends of pathogens to the antibiotic and calculated increases or decreases in pathogens' average resistance rates between 2001 and 2005 higher than or below their resistances in the year 2000.

Gram-positive cocci

- Yearly resistance rates of *Staphylococcus aureus* to tetracycline fluctuated between resistance rates of 37.0% to 59.0% showing a trend which, aside from an initial significant decrease from a resistance rate of 55% in 2000 to 37.0% in 2001, remained stable on the average with minimal fluctuations in yearly resistance rates of between 39% and 59% over the following four years of the study period. *Streptococcus pneumoniae* (α-haemolytic streptococci) showed fluctuations between rates of 14% and 32% in its yearly resistance rates to tetracycline with a trend that demonstrated significant increases in resistance over the six-year period over which data were collected.
- *Streptococcus pyogenes* (β-haemolytic streptococci) demonstrated yearly resistance rates of 36% and 51% to tetracycline which significantly remained stable with little yearly fluctuation within the period for which data were investigated.
- Non-haemolytic streptococci (enterococci and non-enterococcal streptococci) exhibited variations in yearly resistance rates which showed an initial significant decrease from a high resistant rate of 69% in 2000 to a lower rate of 43.6% in 2001 and thereafter remained stable on the average with minimal yearly fluctuations between rates of 50% and 55% over the following four years of the study period.
- *Streptococcus pyogenes* (β-haemolytic streptococci) and *S. pneumoniae* (α-haemolytic streptococci) showed increases of 5.4% and 11.8% respectively in their average resistance rates to tetracycline from 2001 to 2005 higher than their yearly resistance rates in 2000.
- *Staphylococcus aureus* and non-haemolytic streptococci showed decreases of 6.2% and 14.7% in their average resistance rates for the period 2001 to 2005 below their year 2000 resistance rates.

Gram-negative bacilli

- Gram-negative bacilli generally exhibited high yearly resistance rates to tetracycline, demonstrating trends in resistance rate variation that remained stable over the 2000 to 2005 period for which data were analysed.
- *Escherichia coli* showed a significant increase in its resistance rate of 7% in 2000 to 68% in 2001 and thereafter remained stable over the rest of the six-year period.
- *Klebsiella* spp demonstrated a high resistance rate of between 58% and 72% to tetracycline which remained stable at that level over the 2000 to 2005 period for

Table 4.2.10 Yearly percentage pathogen resistances to TETRACYCLINE from Jan 2000 to Dec 2005

Pathogen	Frequencies of pathogen sensitivity testing against antibiotics and calculated percentage resistances and increase in resistan																	
	Jan to Dec 2000			Jan to Dec 2001			Jan to Dec 2002			Jan to Dec 2003			Jan to Dec 2004			Jan to Dec 2005		
	T	R	%R	T	R	%R	T	R	%R	T	R	%R	T	R	%R	T	R	%R
α- Haemolytic strep (S. pneumoniae Viridans Strep	14	2	14	20	2	10	9	1	11	18	6	33	14	6	43	22	7	32
β-Haemolytic strep (S. pyogenes)	23	9	39	19	10	53	12	6	50	11	4	36	19	9	47	14	5	36
Non-haemolytic srep (Enterococci spp)	12	8	67	38	16	42	14	7	50	20	13	65	18	11	61	12	7	58
Neisseria spp	4	1	25	1	0	0	0	0	0	1	0	0	0	0	0	4	1	25
S. aureus	171	94	55	164	61	37	81	48	59	219	128	58	208	107	51	237	93	39
S. albicans	2	2	100	2	1	50	3	3	100	13	8	62	7	6	86	2	1	50
S. albus	12	6	50	7	3	43	5	3	60	15	11	73	17	12	71	12	6	50
S. faecalis	1	1	100	1	1	100	4	3	75	5	4	80	1	0	0	2	0	0
Escherichia coli	207	14	7	310	210	68	252	181	72	159	109	59	147	98	67	114	77	68
Klebsiella spp	46	28	61	58	37	64	38	22	58	50	29	58	1	1	100	25	18	72
Pseudomonas spp	6	5	83	13	10	77	11	11	100	7	6	85	11	9	82	3	2	67
Proteus spp	20	16	80	19	16	84	22	15	68	50	21	75	21	15	71	15	12	80

Table 4.2.11 Yearly percentage pathogen resistances to CO-TRIMOXAZOLE from Jan 2000 to Dec 2005

Pathogen	Frequencies of pathogen sensitivity testing against antibiotics and calculated percentage resistances and increase in resistances																	
	Jan to Dec 2000			Jan to Dec 2001			Jan to Dec 2002			Jan to Dec 2003			Jan to Dec 2004			Jan to Dec 2005		
	T	R	%R	T	R	%R	T	R	%R	T	R	%R	T	R	%R	T	R	%R
α- Haemolytic strep (S. pneumoniae, Viridans strep.	10	9	90	12	8	67	8	4	50	18	10	56	25	21	84	10	9	90
β-Haemolytic strep (S. pyogenes)	13	13	100	12	9	75	5	3	60	13	10	77	12	9	75	5	3	60
Non-haemolytic strep (Enterococci spp)	9	6	67	10	7	70	20	8	40	18	11	61	20	15	75	8	7	88
S. aureus	191	108	57	187	110	59	75	53	71	215	117	54	195	113	58	110	93	85
S. albicans	3	3	100	2	1	50	3	2	67	6	2	33	7	5	71	4	3	75
S. albus	9	6	67	8	6	75	4	0	0	15	10	67	17	13	76	7	6	86
Escherichia coli	169	87	51	163	101	62	76	33	43	129	94	73	94	69	73	56	44	79
Klebsiella spp	47	26	55	82	59	72	19	15	79	52	25	48	52	31	60	26	20	77
Pseudomonas spp	9	7	78	4	3	75	13	10	77	24	21	88	8	8	100	8	7	88
Proteus spp	63	54	86	50	31	62	25	16	64	82	54	66	71	44	62	51	38	75

ABREVIATIONS: T: Total number of pathogens tested in year; R: Number of pathogens resistant; %R: Yearly percentage resistance or yearly rate of resistance

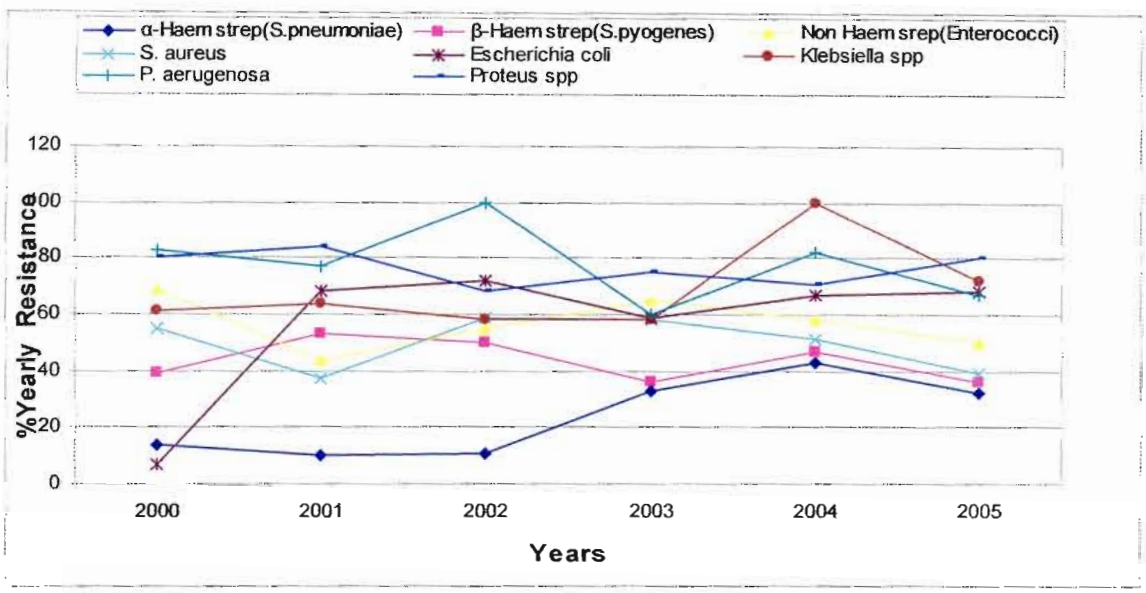

Fig 4.2.22 (a) Yearly variations in percentage pathogen resistances to **Tetracycline** from year 2000 to 2005

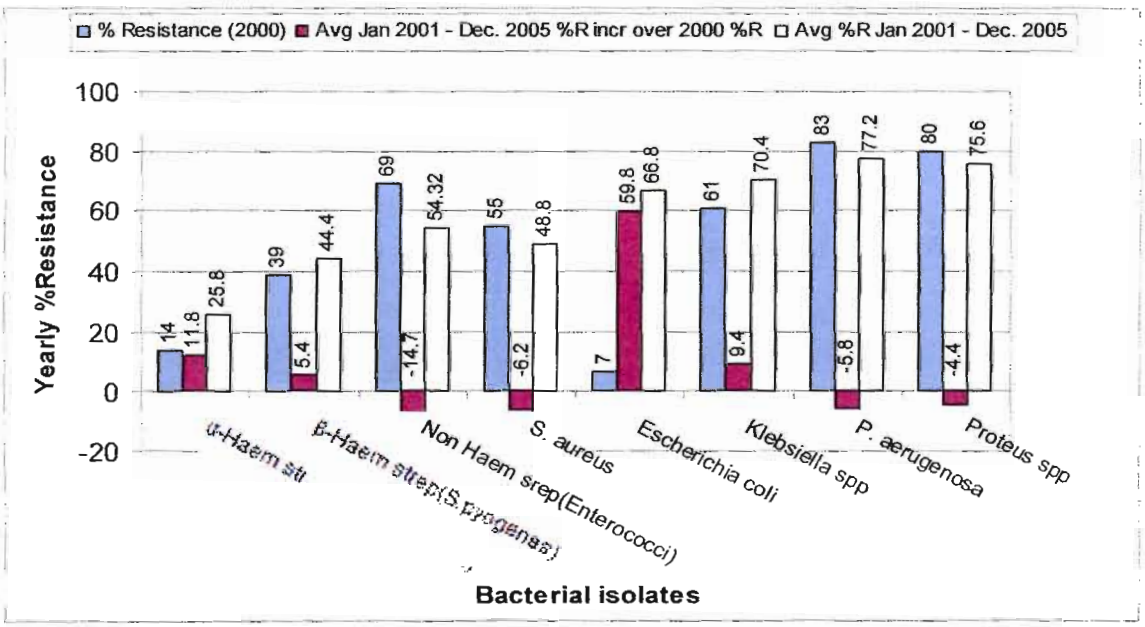

Fig 4.2.22(b) Pathogen yearly resistances to **Tetracycline** showing increases or decreases of pathogens' average resistance rates in 2001-2005 higher than or below their 2000 resistance rates

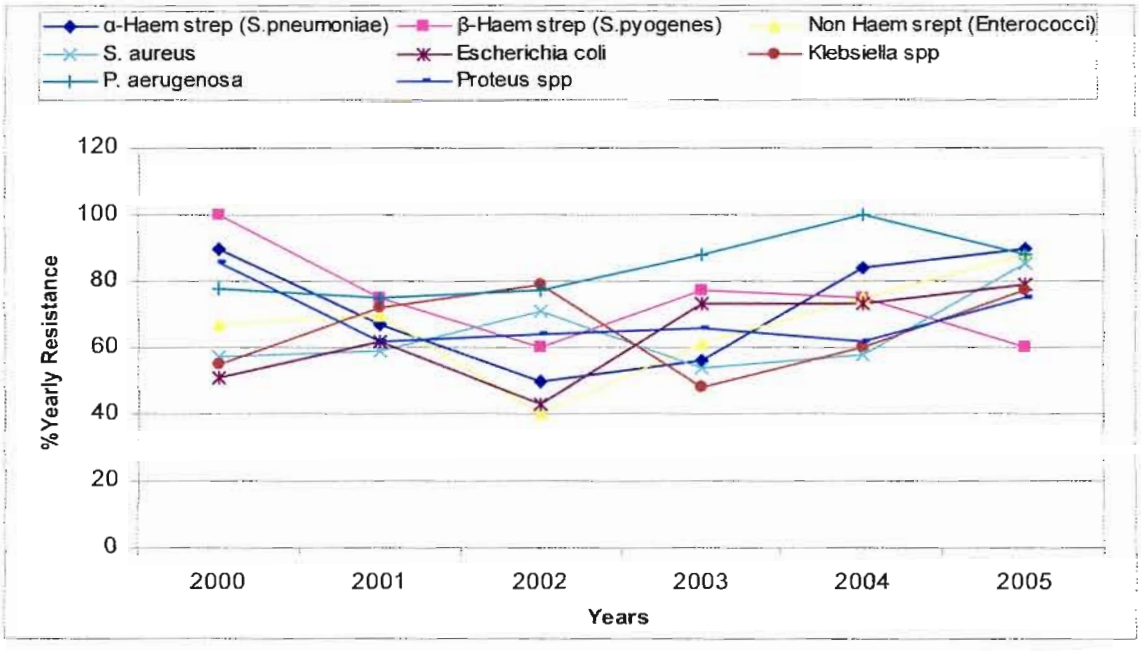

Fig 4.2.23(a) Yearly variations in percentage pathogen resistances to **Co-trimoxazole** from year 2000 to 2005

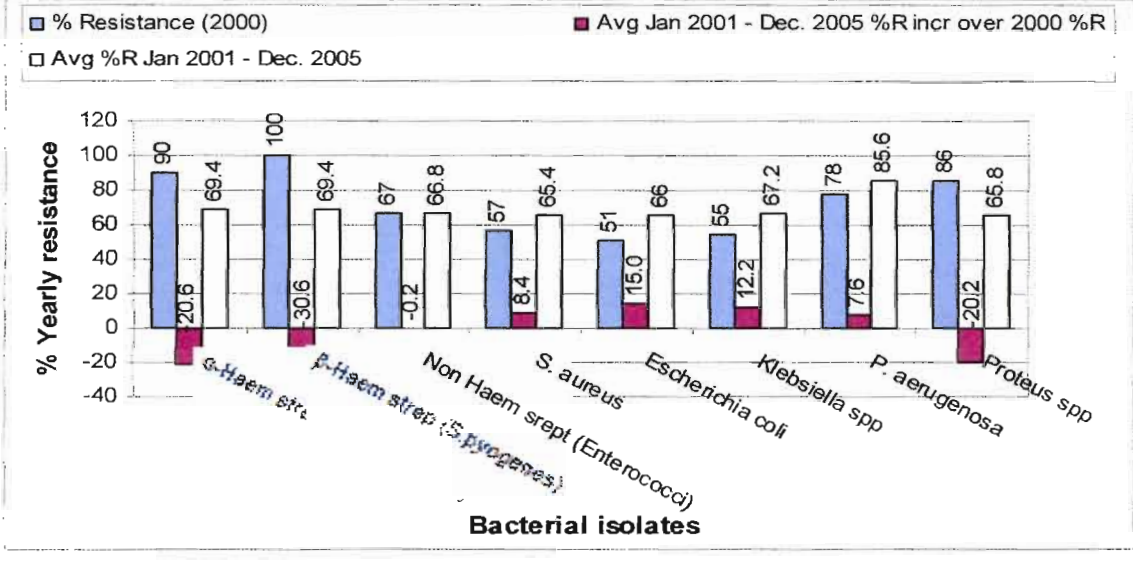

Fig 4.2.23(b) Pathogen yearly resistances to **Co-trimoxazole** showing increases or decreases of pathogens' average resistance rates in 2001-2005 higher than or below their 2000 resistance rates

which data were analysed. A recorded 100% resistance rate in 2004 attributable to an insufficient number of isolates of the organisms tested that year was disregarded in the analysis.

- *Proteus* spp showed a high rate of resistance to tetracycline which remained quite stable at levels of between 71% and 83% higher than the 2000 to 2005 study period but with a trend that demonstrated reduction in yearly resistance over the six-year study period.
- *Pseudomonas* spp showed erratic variations in yearly resistance rates at high levels of between 67% and 100% and with a trend that showed reduction in resistance over the six-year period.
- Average resistance rates of *Escherichia coli* and *Klebsiella* spp to tetracycline for the period 2001 to 2005 showed respective increases of 59.8% and 9.4% higher than the organism's year 2000 resistance rates. *Proteus* and *Pseudomonas* spp on the other hand demonstrated decreases of 4.4 and 5.8% respectively in their average resistance rates to the antibiotic from 2001 to 2005 below their year 2000 resistance rates.

- **Co-trimoxazole**

Variations in yearly resistance rates of bacterial isolates to co-trimoxazole over the period 2000 to 2005 as well as increases or decreases in average resistance rates of pathogens' resistances in the period 2001 to 2005 higher than or below their resistances in year 2000 are shown in Figures 4.2.22 (a) and 4.2.22 (b).

Gram-positive cocci

- *Streptococcus* spp generally exhibited similar trends in the variations of their yearly resistance rates to co-trimoxazole over the specified period of study, showing significant high rates of resistance in year 2000 [100%, 90% and 69% respectively for *Streptococcus pyogenes, Streptococcus pneumoniae* (β- and α- haemolytic streptococci) and non-haemolytic streptococci] which progressively reduced to lower levels in 2002 [60%, 50% and 40% in that order again for *S. pyogenes* and *S. pneumoniae* (β- and α- haemolytic streptococci) and non-haemolytic streptococci] and there after, all three types of streptococci in that same order exhibited increased rates of resistance to the antibiotic, reaching average high resistance levels of 71%, 77% and 75% over the years 2003 to 2005.

- *Staphylococcus aureus* demonstrated high yearly resistances to co-trimoxazole that varied between 54% and 84% with a trend which generally showed increasing yearly resistances of the pathogen to the antibiotic over the 2000 to 2005 period for which pathogen sensitivities to antibiotics were studied.

- Average resistance rates of *Streptococcus pyogenes, Streptococcus pneumoniae* and non-haemolytic streptococci to co-trimoxazole from 2001 to 2005 showed respective decreases of 30.6%, 20.6% and 0.2% below their year 2000 resistance rates. Average resistance rates of *Staphylococcus aureus* to the antibiotic from 2001 to 2005 showed an increase of 8.4% higher than its year 2000 resistance rates.

Gram-negative bacilli

- *Escherichia coli* and *Klebsiella* spp on average showed progressive increases in their yearly resistances to co-trimoxazole that varied respectively between 43% and 79% for *E. coli* and 48% and 79% for Klebsiella over the 2000 to 2005 period of study. This is in the exception of decreased yearly resistance rates of 43% and 48% for the two pathogens in 2002.
- *Pseudomonas* spp showed progressive increases in yearly resistance rates to co-trimoxazole which varied between 75% and 100% over the period for which data were analysed.
- *Proteus* spp, unlike other GNB, on average demonstrated a stable trend in its resistance to co-trimoxazole with resistance rates varying between 62% and 75%. This followed an initial reduction from an 86% resistance rate in 2000 to a 62% resistance rate in 2001 and a resumption of increasing resistance to the antibiotic beginning to manifest from year 2004.
- Average resistance rates of *Escherichia coli*, *Klebsiella* spp and *Pseudomonas* spp to co-trimoxazole from 2001 to 2005 showed increases of 15% each for the *E. coli and Klebsiella* spp and 7.6% for *Pseudomonas* spp higher than their year 2000 resistance rates. Average resistance rates of *Proteus* spp to the co-trimoxazole from 2001 to 2005 on the other hand showed a decrease of 20.2% below its year 2000 resistance rates.

- **Chloramphenicol**

Variations in yearly resistance rates of bacterial isolates to chloramphenicol over the period 2000 to 2005 are shown in Figure 4.2.23 (a). Figure 4.2.23 (b) on the other hand shows increases or decreases in average resistance rates of pathogens in the period 2001 to 2005 higher than or below their resistances in year 2000.

Gram-positive cocci

- Non-haemolytic streptococci, the only species of streptococci tested regularly against chloramphenicol over the period of study demonstrated low yearly rates of resistance against the antibiotic with a trend that showed progressive reduction in resistance from a recorded 33% rate in 2000 to a 0.0% rate in 2005.
- *Staphylococcus aureus* exhibited over the period yearly resistance rates which varied between 19% and 41% with a trend that showed on average a stable average resistance rate over the period for which culture sensitivity results data were studied.
- Average resistance rates of *Staphylococcus aureus* and non-haemolytic streptococci to the chloramphenicol from 2001 to 2005 showed decreases of 10.2% for *Staphylococcus aureus* and 23% for non-haemolytic streptococci below the two pathogens' resistance rates in year 2000.

Gram-negative bacilli

- Gram-negative bacilli organisms generally exhibited trends in yearly resistance rate variations that showed either stable or decreasing such rates to chloramphenicol over the 2000 to 2005 study period.
- *Escherichia coli* and *Klebsiella* exhibited variations in yearly resistance rates to the antibiotic that significantly remained stable within narrow percentage resistance ranges of 36% to 41% and 40% - 56% respectively for the two organisms.
- *Proteus* spp exhibited a trend in resistance variation that showed decreasing rates from 68% to 21% for a greater part of the study period from year 2000 to 2004 after which there was an observed increase to 62% in 2005.
- *Pseudomonas* demonstrated an increase in its resistance to chloramphenicol within the first three years of the study period from 2000 - 2002 at resistance rates that varied from 68% to 93% and thereafter decreased progressively to a resistance rate

Table 4.2.12 Yearly percentage pathogen resistances to **CHLORAMPHENICOL** from Jan 2000 to Dec 2005.

Pathogen	Frequencies of pathogen sensitivity testing against antibiotics and calculated percentage resistances																	
	Jan to Dec 2000			Jan to Dec 2001			Jan to Dec 2002			Jan to Dec 2003			Jan to Dec 2004			Jan to Dec 2005		
	T	R	%R	T	R	%R	T	R	%R	T	R	%R	T	R	%R	T	R	%R
α- Haemolytic strep(S.pneumoniae, Viridans strep)	11	3	27	9	0	0	0	0	0	0	0	0	14	1	7	8	1	13
β-Haemolytic strep (S. pyogenes)	6	2	33	3	1	33	2	0	0	0	0	0	9	3	33	3	0	0
Non-haemolytic strep (Enterococci spp)	3	1	33	16	4	25	5	1	20	4	0	0	9	0	0	3	0	0
Nesseria spp	3	1	33	4	0	0	0	0	0	1	0	0	0	0	0	1	0	0
S. aureus	73	31	42	70	13	19	34	14	41	93	38	41	141	29	21	122	45	37
Escherichia coli	245	100	41	431	172	40	215	109	41	209	78	37	193	70	36	171	63	37
Klebsiella spp	56	26	46	122	68	56	27	11	41	71	26	37	54	23	43	55	22	40
Pseudomonas spp	14	9	64	10	7	70	14	13	93	29	16	55	14	9	64	18	9	50
Proteus spp	59	40	68	77	39	51	30	13	43	88	44	50	180	46	26	91	56	62

Table 4.2.13 Yearly percentage pathogen resistances to **TGCs (CEFOTAXIME/CEFTRIAXONE)** from Jan 2000 to Dec 2005

Pathogen	Frequencies of pathogen sensitivity testing against antibiotics and calculated percentage resistances and increase in resistances																	
	Jan to Dec 2000			Jan to Dec 2001			Jan to Dec 2002			Jan to Dec 2003			Jan to Dec 2004			Jan to Dec 2005		
	T	R	%R	T	R	%R	T	R	%R	T	R	%R	T	R	%R	T	R	%R
S. aureus	69	8	11.6	45	15	33	24	9	37.5	72	38	53	65	15	24	49	16	33
Escherichia coli	129	9	7.9	94	14	15	23	2	9	135	45	33	101	11	11	90	6	7
Klebsiella spp	7	2	29	51	13	25	5	3	60	18	3	17	17	3	18	2	0	0
Pseudomonas spp	25	3	12	27	3	11	56	12	21.4	34	9	26.5	34	6	18	21	3	14.3
Proteus spp	54	3	6	54	3	6	21	4	19	79	10	13	59	2	3.4	58	10	17

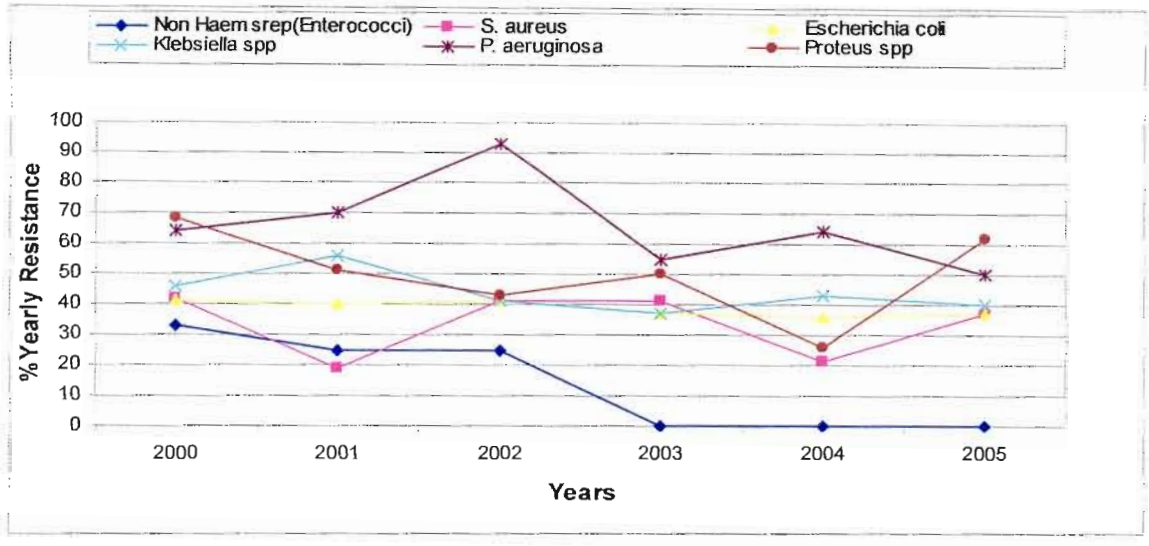

Fig 4.2.24(a) Yearly variations in percentage pathogen resistances to **Chloramphenicol** from year 2000 to 2005

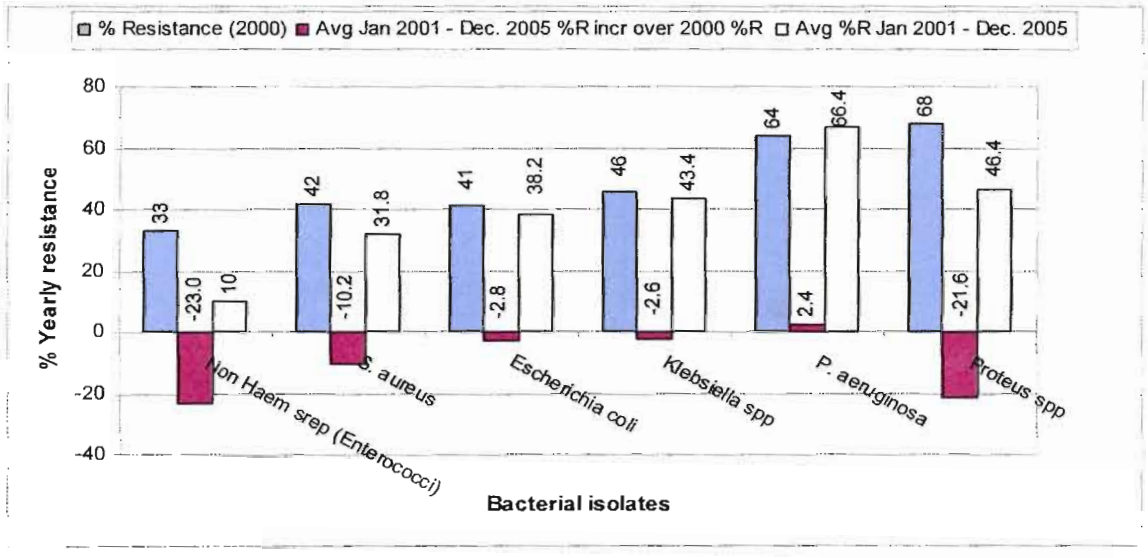

Fig 4.2.24(b) Pathogen yearly resistances to **Chloramphenicol** showing increases or decreases of pathogens' average resistance rates in 2001-2005 higher than or below their 2000 resistance rates

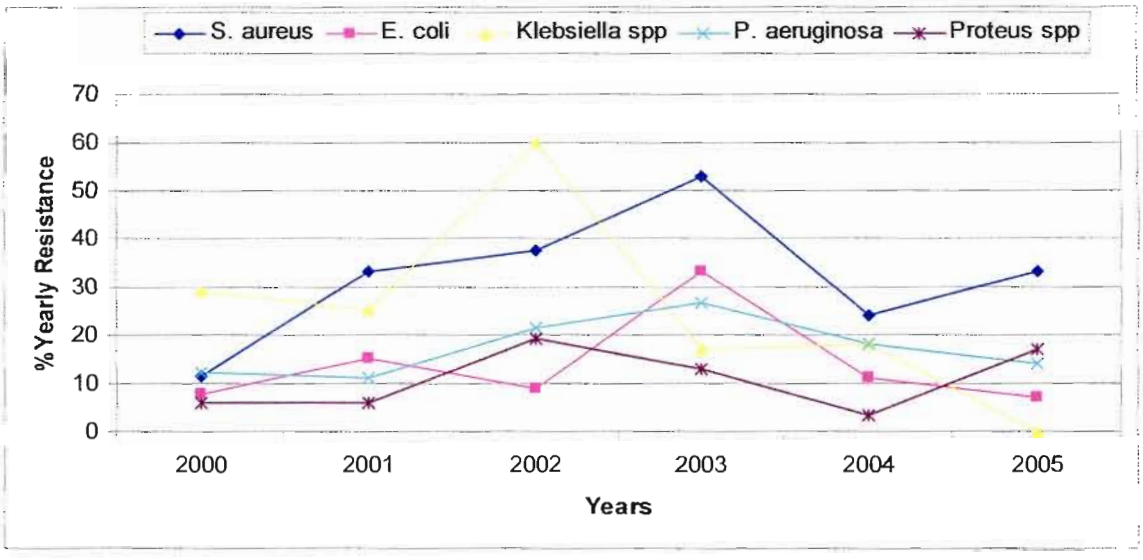

Fig 4.2.25(a) Yearly variations in percentage pathogen resistances to **TGC** from year 2000 to 2005

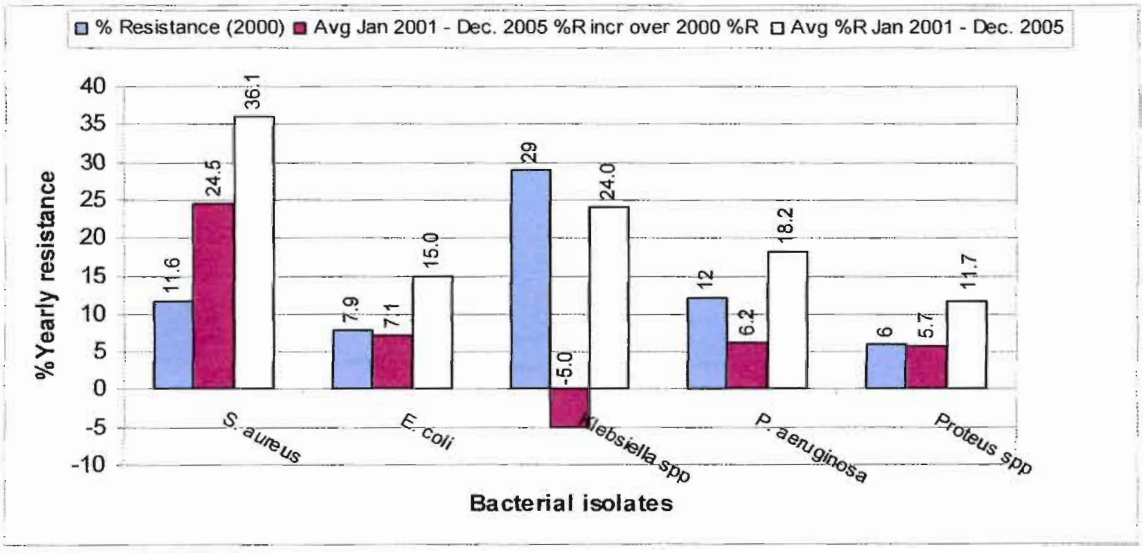

Fig 4.2.25b) Pathogen yearly resistances to **TGCs (Cefotaxime/Ceftriaxone) showing** increases or decreases of pathogens' average resistance rates in 2001-2005 higher than or below their 2000 resistance rates.

of 50%. Except for the significant high resistance rate of 93% recorded in 2002, the pathogens can be said to have exhibited on average decreasing rates in their resistance to chloramphenicol over the six-year period of study at a rate that varied from 68% in 2000 to 50% in 2005.

- Average resistance rates of GNB to chloramphenicol from 2001 to 2005 showed decreases of 2.8%, 2.6% and 21.6% for *Escherichia coli, Klebsiella* and *Proteus* spp respectively and an increase of 2.4% for Pseudomonas below and higher than year 2000 resistance rates for the pathogens

◆ **TGCs (Cefotaxime /Ceftriaxone)**

Figures 4.2.24 (a) and 4.2.24 (b) respectively show variations in yearly resistance rates of bacterial isolates to TGCs (cefotaxime/ceftriaxone) and increases or decreases in average resistance rates of organisms in the period 2001 to 2005 higher than or below their resistances in year 2000. Activities of the third generation cephalosporins (cefotaxime or ceftriaxone) were tested mainly against *Staphylococcus aureus* and gram-negative bacilli (*Escherichia coli, Klebsiella, Proteus* and *Pseudomonas* spp).

Gram-positive cocci

- *Staphylococcus aureus* exhibited yearly resistance rates that showed variations within a range of 11.6% to 53% and with a trend that demonstrated progressive increase in the organisms' yearly resistance to TGCs which reached a peak in 2003 followed by a period of diminished resistance in year 2004 but with a resumption of increasing trend in resistance by 2005.

Gram-negative bacilli

- *Escherichia coli, Klebsiella* and *Pseudomonas* spp showed increasing yearly resistance rates to the TGCs that reached a maximum, (33% for *Escherichia coli* in 2003, 60% for *Klebsiella* in 2002, and 26% for *Pseudomonas* in 2003), followed by years of diminishing resistances reaching minimum rates of resistance (0.0% for *Klebsiella*, 7.0% for *Escherichia coli* and 14.0% for *Pseudomonas*) in 2005.
- *Proteus* spp, like *Staphylococcus, aureus* demonstrated a trend in the variation of their yearly resistance rates to the antibiotic. The organisms showed increasing resistances to the antibiotic from a 6% rate in 2000 to a maximum rate of 19% in

2002, thereafter progressively decreased to a minimum of 3.4% in 2004 whence it resumed again an increasing trend in resistance.

- Average resistance rates of all four GNB to TGCs from 2001 to 2005 showed increases of 7.1%, 6.2% and 5.7% for *Escherichia coli, Pseudomonas* and *Proteus* spp respectively and a decrease of 5% for *Klebsiella* higher than and below year 2000 resistance rates.

♦ Gentamicin

Variations in yearly resistance rates of bacterial isolates to gentamicin over the period 2000 to 2005 are shown in Figure 4.2.25 (a). Figure 4.2.25 (b) depicts increases or decreases in average resistance rates of organisms to the antibiotic in the period 2001 to 2005 higher than or below their resistance rates in year 2000.

Gram-positive cocci

- Non-haemolytic streptococci (enterococci and non-enterococci), the only streptococci tested regularly against gentamicin, demonstrated percentage yearly resistances in the range of 14% to 66.7% against the antibiotic with a trend that showed progressive increases in yearly resistance rates over the 2000 to 2005 period of study.
- *Staphylococcus aureus* demonstrated yearly resistance rates that varied within a 25% to 42% range with a trend that showed slight increases in resistance by year 2005.
- Average yearly resistance rates of non-haemolytic streptococci and *Staphylococcus aureus* to the antibiotic from 2001 to 2005 showed increases of 26.5% and 6.8%, higher than and below their year 2000 resistance rates.

Gram-negative bacilli

- All GNB on average exhibited yearly resistance rates which generally remained stable within narrow ranges of yearly resistance rates over the six-year period over which pathogens' sensitivity patterns to antibiotics were studied. Specifically,
- *Escherichia coli* was seen to exhibit yearly resistance rates which varied within a narrow range of 11% and 18% with a trend that remained very stable over the six-year period of organisms' antibiotic sensitivity data study.

- *Klebsiella* spp exhibited yearly resistance rates to gentamicin which fluctuated within a range of 13% to 39% but demonstrating on average a trend that showed stability in variations of the pathogens yearly resistance rates to the antibiotic.
- *Proteus* spp showed yearly resistance rates which varied within a range of 10% to 30% over the period of study with a trend in resistance variation over the years that show stability in the organisms' resistance to the antibiotic over the study period.
- *Pseudomonas* generally exhibited low yearly resistance rates ranging from 12% to 20% to gentamicin, with a trend in yearly variations in resistance that demonstrated stability in the organisms' resistance to the antibiotic over the six-years period of sensitivity data collection, except for an isolated recorded resistance of 38% in 2002.
- Average resistance rates of *Klebsiella* spp to gentamicin from 2001 to 2005 showed increases of 15% higher than their year 2000 resistance rates. *Escherichia coli*, *Proteus and Pseudomonas* likewise, exhibited decreases of 1.4%, 7.2% and 2.2% in their average yearly resistance rates to the antibiotic from 2001 to 2005 higher than and below their year 2000 resistance rates.

- **Amikacin**

Yearly resistance rates of bacterial isolates to amikacin over the period 2000 to 2005 and also increases or decreases in average resistance rates of organisms in the period 2001 to 2005 higher than or below their resistances in year 2000 are shown in Figures 4.2.26 (a) and 4.2.26 (b) respectively. Reported numbers of bacterial isolates tested against the antibiotic in 2002 are very low in comparison with numbers of isolates tested against it in other years (Table 4.3.15). Reported yearly resistance rates of organisms in 2002 are considered out of range and therefore disregarded. Variations in pathogens' yearly resistance rates to amikacin and increases or decreases in their average resistance rates from 2001 to 2005 higher than or below their year 2000 resistance rates are stated as follows:

Gram-positive cocci

- *Staphylococcus aureus* exhibited yearly resistance rates to amikacin within the narrow range of between 7.0% and 19% with a trend that remained stable over the years of pathogens' antibiotic sensitivity data study.

Table 4.2.14 Yearly percentage pathogen resistances to **GENTAMICIN** from Jan 2000 to Dec 2005

Pathogen	Frequencies of pathogen sensitivity testing against antibiotics and calculated percentage resistances and increase in resistances																	
	Jan to Dec 2000			Jan to Dec 2001			Jan to Dec 2002			Jan to Dec 2003			Jan to Dec 2004			Jan to Dec 2005		
	T	R	%R	T	R	%R	T	R	%R	T	R	%R	T	R	%R	T	R	%R
α- Haemolytic strep(S.pneumoniae, Viridans strept)	7	3	43	12	3	25	1	0	0				2	1	50	2	1	50
β-Haemolytic strep (S. pyogenes)	5	1	20	4	0	0	1	0	0	2	0	0	2	0	0	3		66.7
Non-haemolytic strep (Enterococci spp)	7	1	14	18	6	33	11	3	27	3	1	33	7	3	43	6	4	66.7
S. aureus	77	20	26	97	26	27	65	16	25	113	47	42	97	32	33	60	22	37
S. albus	9	4	44	7	2	29	2	1	50	14	7	50	14	3	21	4	3	75
Escherichia coli	241	40	17	401	67	17	235	25	11	191	32	17	189	29	15	169	31	18
Klebsiella spp	54	7	13	145	46	32	28	11	39	87	24	28	71	16	23	58	11	19
Pseudomonas spp	20	4	20	61	8	13	13	5	38	75	10	13	53	7	13	49	6	12
Proteus spp	54	14	26	71	14	20	39	4	10	88	18	20	95	13	14	89	27	30

Table 4.2.15 Yearly percentage pathogen resistances to **AMIKACIN** from Jan 2000 to Dec 2005

Pathogen	Frequencies of pathogen sensitivity testing against antibiotics and calculated percentage resistances and increase in resistances																	
	Jan to Dec 2000			Jan to Dec 2001			Jan to Dec 2002			Jan to Dec 2003			Jan to Dec 2004			Jan to Dec 2005		
	T	R	%R	T	R	%R	T	R	%R	T	R	%R	T	R	%R	T	R	%R
S. aureus	28	2	7	21	3	14	1	0	0	32	4	13	32	6	19	19	2	11
Acinetobacter	1	1	100	4	1	25	5	1	20	1	0	0	1	1	100	4	0	0
Escherichia coli	25	0	0	34	0	0	4	2	50	27	3	11	34	7	21	16	3	19
Klebsiella spp	15	0	0	35	1	3	6	0	0	20	2	10	15	2	13	8	0	0
Pseudomonas spp	18	6	33	37	1	3	3	1	33	49	0	0	50	4	8	52	1	2
Proteus spp	8	0	0	17	2	12	2	1	50	21	2	10	18	3	17	26	0	0

ABREVIATIONS: T: Total number of pathogens tested in year; R: Number of pathogens resistant; %R: Yearly percentage resistance or yearly rate of resistance

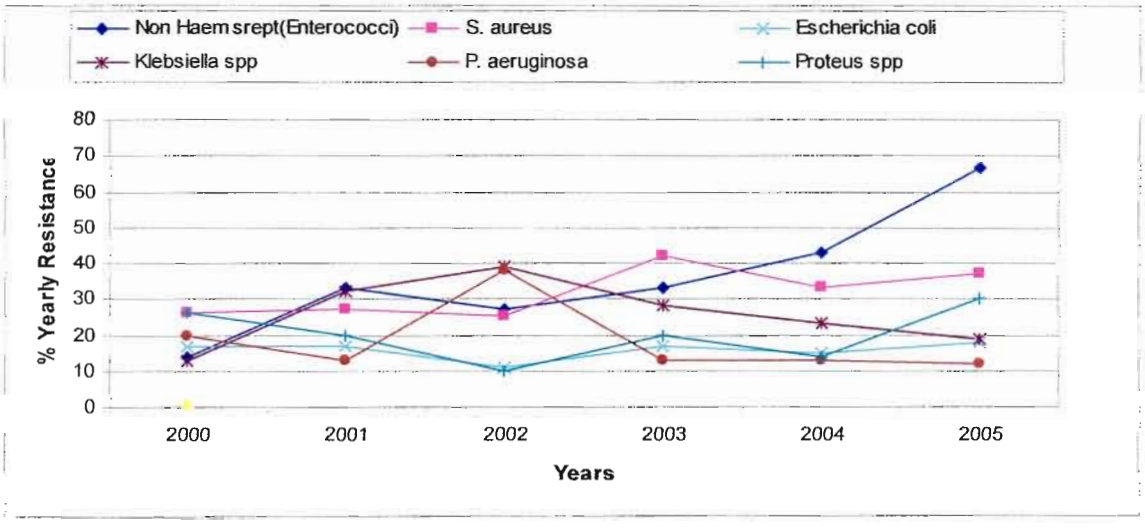

Fig 4.2.26(a) Yearly variations in percentage pathogen resistances to **Gentamicin** from year 2000 to 2005

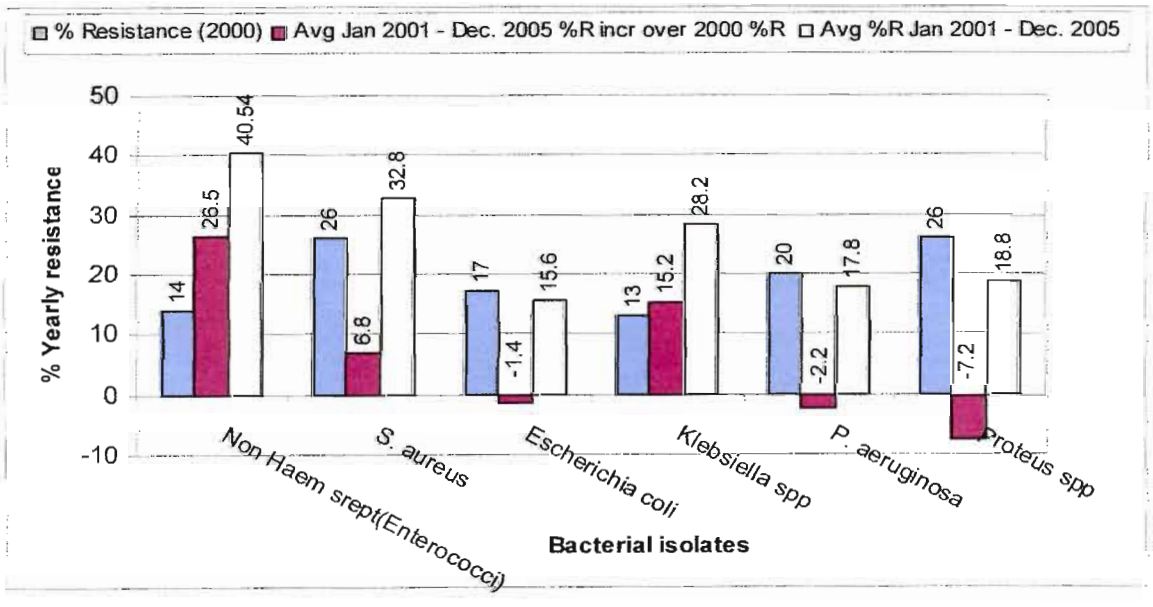

Fig 4.2.26(b) Pathogen yearly resistances to **Gentamicin** showing increases or decreases of pathogens' average resistance rates in 2001-2005 higher than or below their 2000 resistance rates

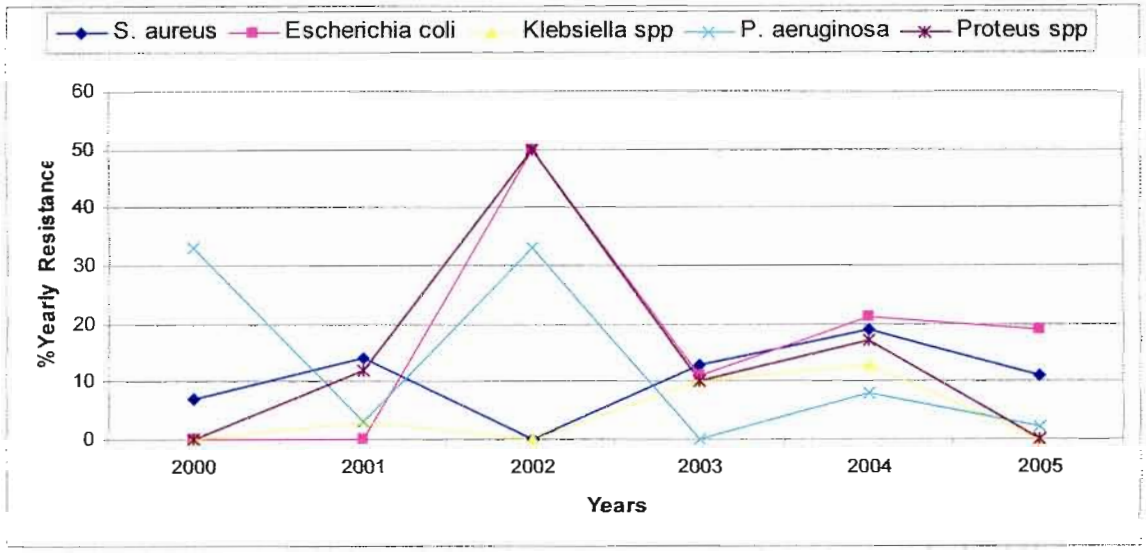

Fig 4.2.27(a) Yearly variations in percentage pathogen resistances to **Amikacin** from year 2000 to 2005

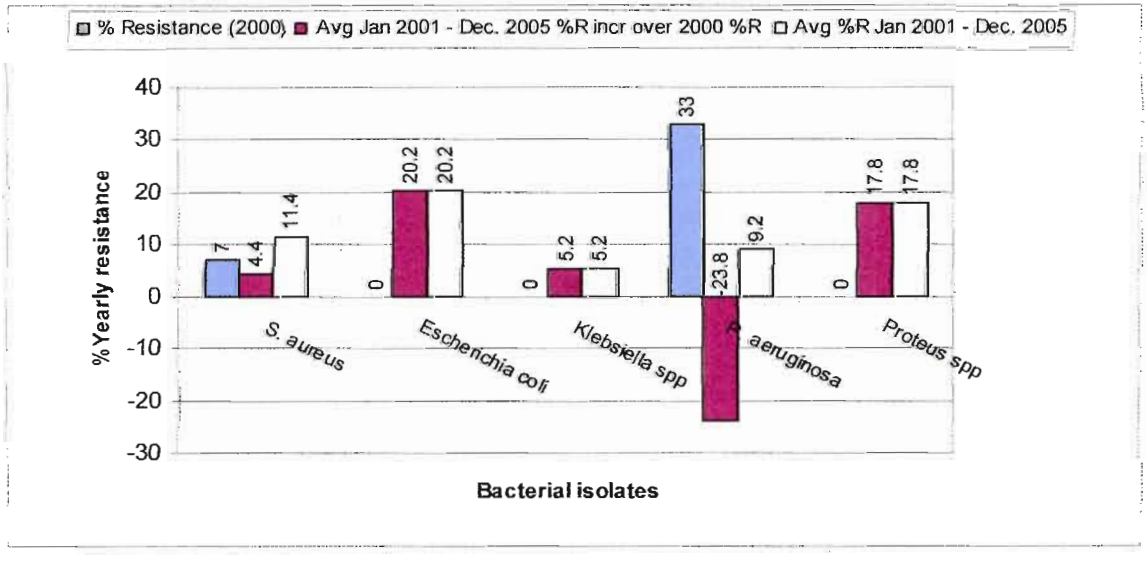

Fig 4.2.27(b) Pathogen yearly resistances to **Amikacin** showing increases or decreases of pathogens' average resistance rates in 2001-2005 higher than or below their 2000 resistance rates

- The average resistance rate of *Staphylococcus aureus* from 2001 to 2004 to amikacin showed an increase of 4.4% higher than the pathogen's year 2000 resistance rate.

Gram-negative bacilli

- *Escherichia coli*, *Klebsiella* spp and *Proteus* spp respectively exhibited resistance rates to amikacin within the narrow ranges of 0.0% to 21%, 0.0% - 13% and 0.0% - 17% which remained stable over the six-years of sensitivity data study.
- *Pseudomonas* spp showed yearly resistance rates to amikacin that varied within the wider range of 0.0% to 33% and which demonstrated a trend in yearly resistance rate variation showing a fall from a rate of 33% in 2000 to a low stable range of between 0.0% and 8.0% over the rest of the study period.
- Average percentage resistances of *Escherichia coli*, *Klebsiella* and *Proteus* spp to amikacin from 2001 to 2005 respectively showed increases of 20.2%, 5.2% and 17.8% higher than year 2000 resistance rates of the pathogens. *Pseudomonas* spp showed a decrease of 23.8% in their average yearly resistance rate from 2001 to 2005 below their year 2000 resistance rates.

◆ **Ciprofloxacin**

Variations in yearly resistance rates of bacterial isolates to ciprofloxacin over the period 2000 to 2005 are shown in Figure 4.2.27 (a). Figure 4.2.27 (b) on the other hand shows increases or decreases in average percentage resistances of organisms in the period 2001 to 2005 higher than or below their resistances in year 2000. Reported percentage resistance for *Staphylococcus aureus* for year 2003, *Proteus* spp for year 2002, *Pseudomonas* spp 2002 and *Klebsiella* for years 2002 and 2005 (Table 4.3.16) may be disregarded on the basis of determined resistance rates being out of range of rates determined for other years due to few frequencies of testing the isolates in those years.

Gram-positive bacteria

- *Staphylococcus aureus* is seen to exhibited yearly resistance rates to ciprofloxacin in the range of 13% to 32% with a trend that showed a decline in the resistance of the organism to the antibiotic over the 2000 to 2005 study period.
- The average yearly resistance rate of *Staphylococcus aureus* over 2001 to 2005 decreased by 5.0% below the pathogen's resistance rate in the year 2000.

Table 4.2.16 Yearly percentage pathogen resistances to **CIPROFLOXACIN** from Jan 2000 to Dec 2005

Pathogen	Frequencies of pathogen sensitivity testing against antibiotics and calculated percentage resistances and increase in resistances																	
	Jan to Dec 2000			Jan to Dec 2001			Jan to Dec 2002			Jan to Dec 2003			Jan to Dec 2004			Jan to Dec 2005		
	T	R	%R	T	R	%R	T	R	%R	T	R	%R	T	R	%R	T	R	%R
Staphylococcus aureus	19	6	32	22	5	23	52	16	31	4	2	50	22	4	18	23	3	13
Escherichia coli	20	2	1	24	10	42	23	2	9	56	10	18	28	9	32	30	4	13
Klebsiella spp	8	3	38	36	18	50	6	1	17	23	11	48	15	8	53	7	0	0
Pseudomonas spp	19	1	5	40	8	20	6	0	0	55	6	11	30	1	3	7	0	0
Proteus spp	10	2	20	15	4	27	5	0	0	26	6	23	13	3	23	17	0	0

Table 4.2.17 Yearly percentage pathogen resistances and increases in resistances to formulary antibiotics from Jan 2000 to Dec 2005 at all study sites - **NALIDIXIC ACID**

Pathogen	Frequencies of pathogen sensitivity testing against antibiotics and calculated percentage resistances and increase in resistances																	
	Jan to Dec 2000			Jan to Dec 2001			Jan to Dec 2002			Jan to Dec 2003			Jan to Dec 2004			Jan to Dec 2005		
	T	R	%R	T	R	%R	T	R	%R	T	R	%R	T	R	%R	T	R	%R
Staphylococcus aureus	8	4	50	13	9	69	13	8	61	24	17	70.3	17	9	53	6	3	50
Escherichia coli	110	19	17	313	52	17	180	34	19	154	36	23	101	32	32	91	13	14
Klebsiella spp	27	5	19	60	9	15	34	5	15	41	11	27	29	9	31	16	4	25
Pseudomonas spp	6	2	33	6	2	33	3	1	33	5	2	40	2	1	50	5	2	40
Proteus spp	6	2	33	15	5	33	10	3	30	13	1	8	8	4	50	3	0	0

Table 4.2.18 Yearly percentage pathogen resistances and increases in resistances to formulary antibiotics from Jan 2000 to Dec 2005 - **NITROFURANTOIN**

Pathogen	Frequencies of pathogen sensitivity testing against antibiotics and calculated percentage resistances and increase in resistances																	
	Jan to Dec 2000			Jan to Dec 2001			Jan to Dec 2002			Jan to Dec 2003			Jan to Dec 2004			Jan to Dec 2005		
	T	R	%R	T	R	%R	T	R	%R	T	R	%R	T	R	%R	T	R	%R
β-Haemolytic strep (S. pyogenes)	1	1	100	7	1	14	6	2	33	3	0	0	5	1	20	3	3	100
Staphylococcus aureus	8	1	13	15	6	40	6	0	0	20	8	40	36	10	28	11	1	9
Escherichia coli	98	13	13	309	38	12	181	37	20	145	27	19	115	18	16	67	6	9
Klebsiella spp	27	5	19	58	12	21	28	11	39	43	12	28	38	7	18	11	2	18
Pseudomonas spp	5	3	60	5	3	60	2	1	50	5	4	80	2	1	50	1	0	0
Proteus spp	5	3	60	13	11	85	9	7	78	18	7	39	10	6	60	1	1	100

ABREVIATIONS: T: Total number of pathogens tested in year; R: Number of pathogens resistant; %R: Yearly percentage resistance or yearly rate of resistance

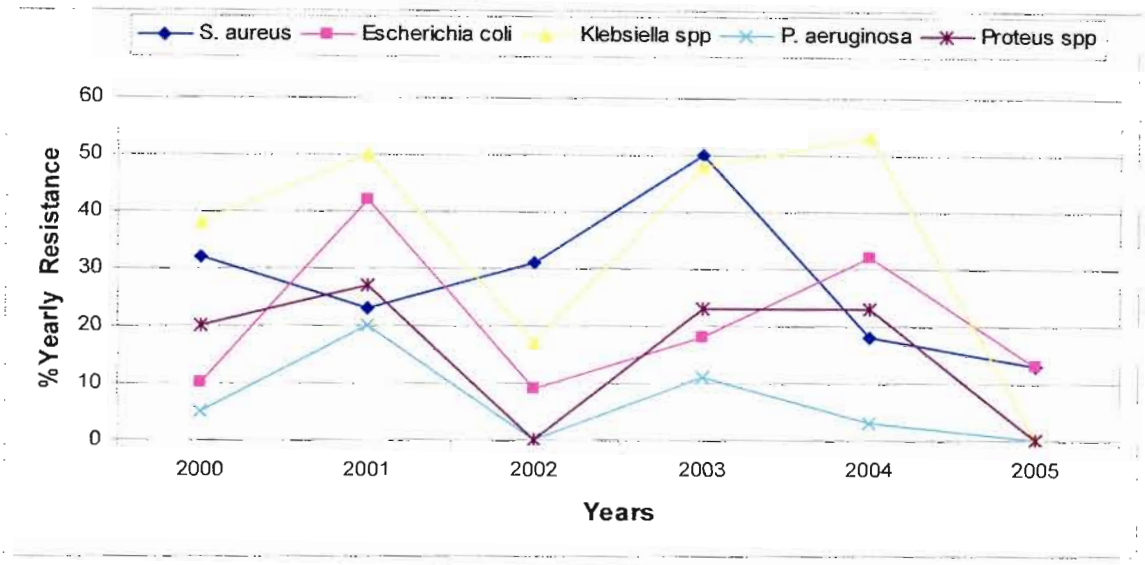

Fig 4.2.28(a) Yearly variations in percentage pathogen resistances to **Ciprofloxacin** from year 2000 to 2005

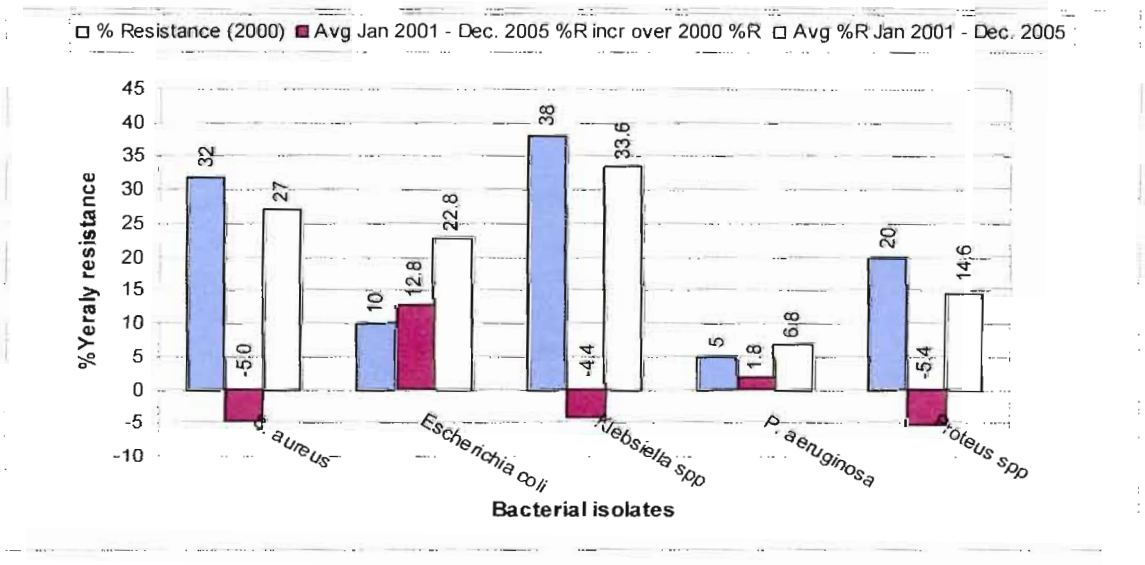

Fig 4.2.28(b) Pathogen yearly resistances to **Ciprofloxacin** showing increases or decreases of pathogens' average resistance rates in 2001-2005 higher than or below their 2000 resistance rates

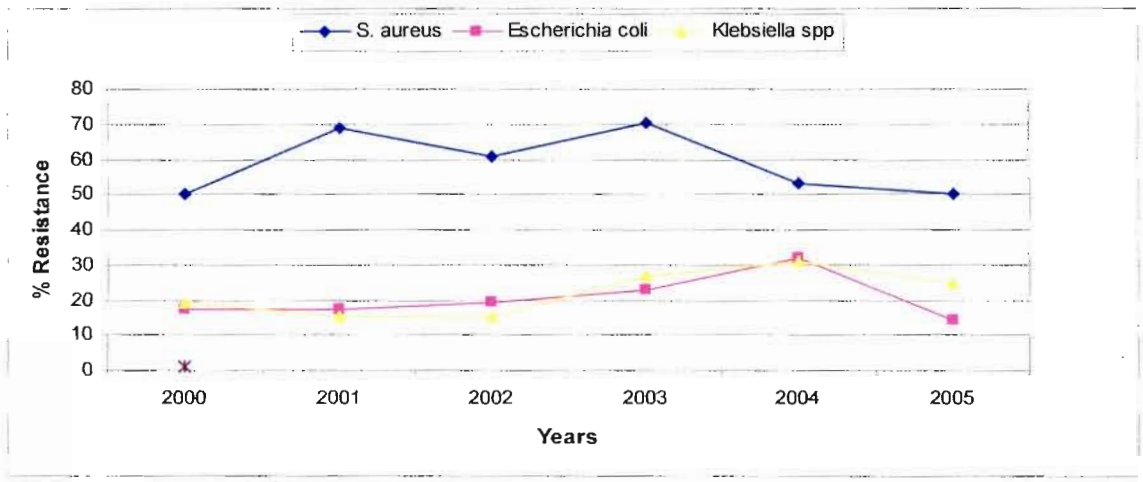

Fig 4.2.29(a): Yearly variations in percentage pathogen resistances to **Nalidixic acid** from year 2000 to 2005

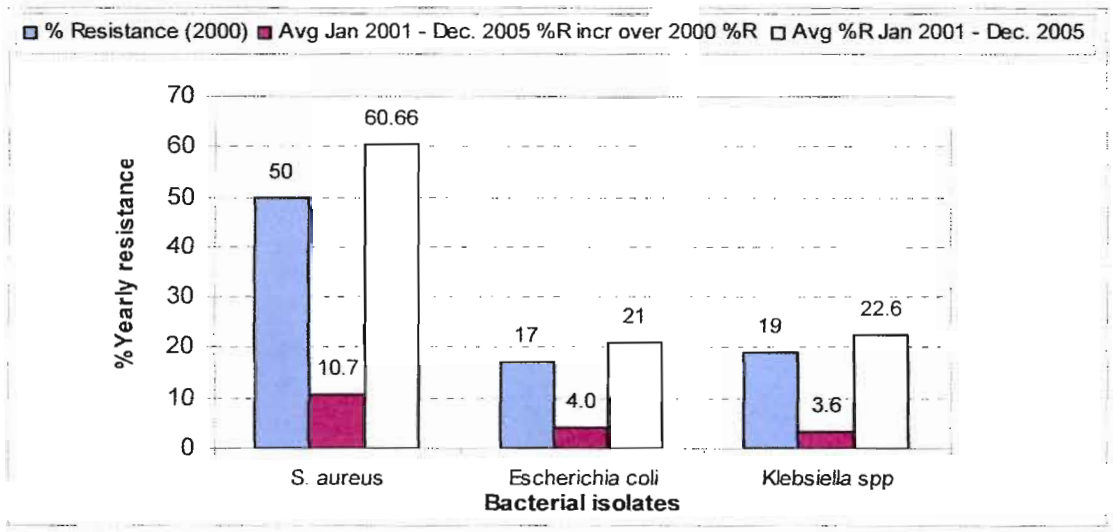

Fig 4.2.29b) Pathogen yearly resistances to **Nalidixic acid** showing increases or decreases of pathogens' average resistance rates in 2001-2005 higher than or below their 2000 resistance rates

Gram-negative bacilli

- *Escherichia coli* showed yearly resistance rates in the range of 9% to 42% to ciprofloxacin with an erratic trend in variation over the years that can neither be described as decreasing nor increasing.

  Proteus spp, demonstrated resistance rates to the antibiotic range of 0.0 - 27% with a variation in trend that was stable in the range of 20% to 27% from 2000 to 2004 after which there was a decline in the resistance of the organism to the antibiotic.
- *Klebsiella* spp, exhibited a yearly resistance rate to the antibiotic in the range of 0.0% to 53% with a variation in trend that showed an increase in yearly resistance rates from 2000 to a stable rate resistance range of 50% to 53% from 2001 to 2004 after which there was a decline in the resistance of the organism to the antibiotic.
- *Pseudomonas* spp similarly exhibited yearly resistances to the antibiotic in the range of 0.0% to 20% with a trend that on the average they demonstrated stability in variation over the years of pathogen antibiotic sensitivity study.
- Average yearly resistances of *Escherichia coli* and *Pseudomonas* to ciprofloxacin from 2001 to 2005 showed increases of 12.8% and 1.8% respectively higher than the pathogens' yearly resistance rates in 2000 while *Klebsiella* and *Proteus* spp respectively showed decreases of 4.4% and 5.4% in the average yearly resistances for the same time period below their yearly resistance rates in year 2000.

◆ **Nalidixic acid**

Yearly resistance rates of bacterial isolates to nalidixic acid over the period 2000 to 2005 and also increases or decreases in average resistance rates of organisms in the period 2001 to 2005 higher than or below their resistances in year 2000 are shown in Figures 4.3.48 (a) and 4.3.48 (b) respectively.

Gram-positive cocci

- *Staphylococcus aureus* exhibited high yearly percentage resistances against nalidixic acid in the range of 50% to 73% with a trend in yearly percentage resistance variation that on average showed stability in its resistance to the antibiotic over the period of pathogens' antibiotic sensitivities assessment study.
- Average yearly resistance rates of *Staphylococcus aureus* to nalidixic acid from 2001 to 2004 increased by 10.7% higher than its resistance rate in year 2000.

Gram-negative bacilli

- *Escherichia coli* and *Klebsiella* spp respectively exhibited yearly resistance rates in the ranges of 17% to 32%, 15% to 31% to nalidixic acid. They also displayed similar trends in variations of their yearly percentage resistances to the antibiotic which on average remained stable over the six-year period of pathogen antibiotic sensitivity study but with indicates of distinctive gradual increases in resistance rates from 2002 to 2004 after which there were diminutions.
- The average yearly resistance rates of *Escherichia coli* and *Klebsiella* spp to nalidixic acid from 2001 to 2004 increased by 4.6% and 3.6% respectively, 10.7% higher than their resistance rates in year 2000.
- *Proteus* spp and *Pseudomonas* spp were tested for few times only against nalidixic for all years. Yearly resistance rates determined from such low frequencies of testing the organisms against the antibiotic were considered not representative of the pathogens' actual resistances to the antibiotic for their use in determining variations in yearly resistances of the organisms to the antibiotic.

◆ **Nitrofurantoin**

Variations in yearly resistance rates of bacterial isolates to nitrofurantoin over the period 2000 to 2005 are shown in Figure 4.2.29 (a). Figure 4.2.29 (b) shows increases or decreases in average resistance rates of organisms in the period 2001 to 2005 higher than or below their resistances in the year 2000. 0.0% percentage resistances reported for *Staphylococcus aureus* in year 2002 and 100% for *Proteus* in 2005 was determined from insufficient data and accordingly disregarded in yearly percentage resistance variation trend determinations.

Gram-positive cocci

- *Staphylococcus aureus* showed yearly resistance rates in the range of 13% to 40% to nitrofurantoin by this consideration were seen to be in the range of 13% to 40% with a corresponding trend in the variation of its yearly resistance rate to the antibiotic that showed increases from year 2000 to 2003 after which there were progressive decreases to a rate of 18% in 2005.
- Average yearly resistance rates of *Staphylococcus aureus* to nalidixic acid from 2001 to 2004 increased by 10.4 % higher than its resistance rate in year 2000.

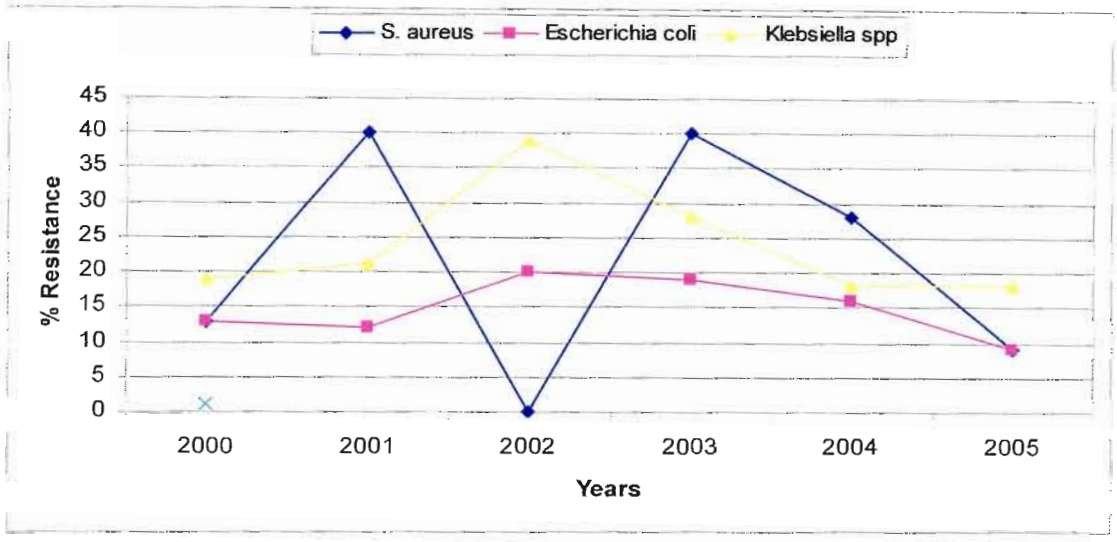

Fig 4.2.30(a): Yearly variations in percentage pathogen resistances to **Nitrofurantoin** from year 2000 to 2005

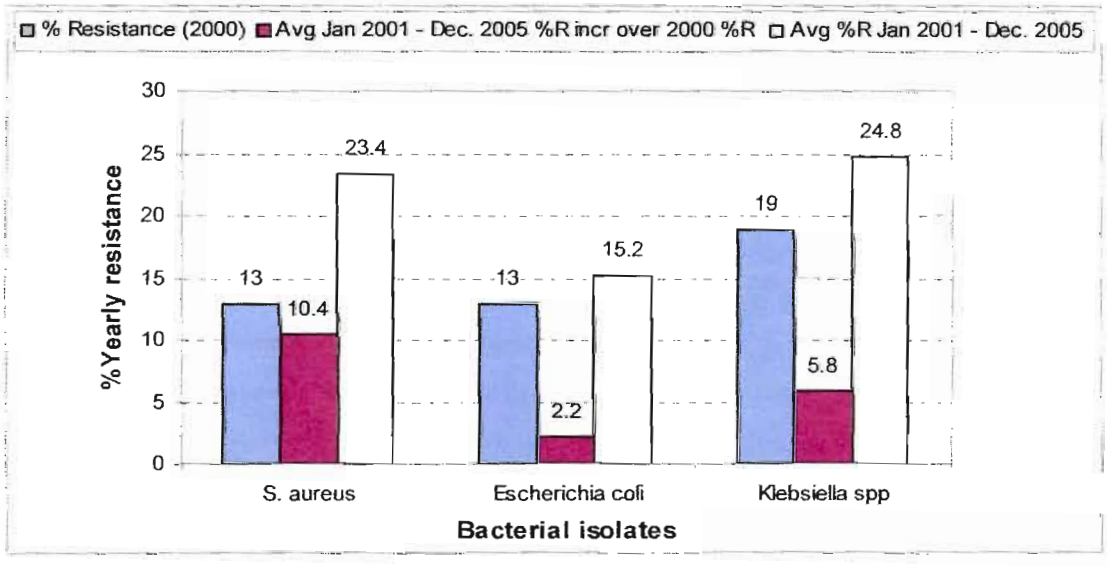

Fig 4.2.30(b): Pathogen yearly resistances to **Nitrofurantoin** showing increases or decreases of pathogens' average resistance rates in 2001-2005 higher than or below their 2000 resistance rates

Gram-negative bacilli

- *Escherichia coli* and *Klebsiella* species respectively exhibited yearly resistance rates in the ranges of 9% to 20% and 18% to 28% to nitrofurantoin and displayed similar trends in yearly resistant rate variation to the antibiotic nitrofurantoin. The two organisms both showed progressive increases in their resistance to the antibiotic from year 2000 reaching maximum yearly resistance rates in 2002 which then decreased uniformly to minimum values in 2005.
- Average yearly resistance rates of *Escherichia coli, Klebsiella* spp and *Proteus* spp to nitrofurantoin from 2001 to 2004 increased by 2.2% and 5.8% and 12.4% respectively higher than their resistance rates in year 2000.
- *Proteus* spp and *Pseudomonas* spp, as in the case of nalidixic acid were tested for too few times against nitrofurantoin for all years for yearly resistance rates to be determined in a way representative of the pathogens' actual resistances to the antibiotic.

4.2.3.2.2 Results Evaluation and Discussion

- **Bacteria pathogen antibiotic resistance development: The impact of antibiotic use**

A resistant strain of an organism to a given antibiotic can colonise and become selected for growth in a person taking the given antibiotic. The mechanism involved manifests through the wiping out of non-resistant strains of the organism and other susceptible flora that ordinarily keep the growth of resistant strains of the organism in check in the person before the use of the antibiotic (Colgan & Powers, 2001:999). The process is referred to as antibiotic "selective pressure" and results in the emergence of resistant strains of the bacteria in question within the population in which the antibiotic is prescribed. According to Colgan and Powers (2001:999), when antibiotics are prescribed to large numbers of persons in a population, resistant strains of the bacteria may become the dominant strains in the environment where the antibiotic is used and the bacteria at that point may be described as becoming resistant to the antibiotic in question. The development of antibiotic resistance by mechanisms of selective pressure, the authors further indicated, is a problem associated with antibiotic over-prescription and use within communities or health institutions. It is an impact of antibiotic use that

one can expect to see manifesting when the agents are prescribed and used over protracted periods of time within given clinical environments.

Demonstrating as a reversal of the process of pathogen antibiotic resistance development by selective pressure, bacterial pathogens that have developed acquired resistance to a given antibiotic may lose such resistance and become sensitive again to the antibiotic in the event of such antibiotic being withheld over a period of time and then reintroduced or used at a reduced rate (Gould, 1999:460), On the basis of these and depending on patterns of antibiotic use in given clinical environments, it is possible to observe both increases and decreases in resistance rates of pathogens to given antibiotics over periods of study within which patterns of antibiotic resistance rates of organisms are investigated.

- **Considerations of limitations of aspect of study**

Analysis of culture sensitivity test results data collected from a given environment of antibiotic use to provide reliable information on patterns of organisms' rates of resistance over a given time period, needs to be done with data that are sufficient with respect particularly to frequencies of testing of bacterial isolates over the definite or discrete time period of the data study. Numbers of isolates of organisms tested for their sensitivities against given antibiotics should be large enough to provide sensitivity or resistance rates that can be considered representative of the true sensitivity or resistance rates of the organism to antibiotics against which they are tested. Data from which organisms' percentage resistances were determined for this research lack this quality and it is recognised as a major limitation that has the effect of compromising percentage yearly resistances determined for some organisms against a number of the antibiotics studied. Frequencies of testing of isolates of some organisms against certain antibiotics in some years were found to be too small to make yearly resistance rates calculated from them incomparable with those of years for which larger numbers of such isolates were tested. Plots of organisms' yearly resistance rates against years that were descriptively used to determine increasing or decreasing trends in pathogens' yearly resistance rates to antibiotics in such cases were seen to demonstrate erratic variations in trends which were difficult to interpret. With these limitations, it was found necessary to disregard such out of range data in order to establish in such cases, trends in variations of the yearly resistance rates of the affected organisms to the given antibiotics that could be

interpreted to establish whether or not the organisms demonstrate increasing, decreasing or stable resistances to the given antibiotics over the period of study.

As a means of validating inferences on increasing or decreasing trends in organisms' yearly resistance rates, average percentage yearly resistances of organisms to given antibiotics over the period 2001 to 2005 were determined and compared to their resistance rates in year 2000 taken as baseline yearly resistance rate values. The comparison enables a determination of whether there had been increases or decreases in organisms' resistance rates over the years following the year for which baseline yearly resistance rate values were established. Calculated increases or decreases of organisms' average yearly resistance rates in the period 2001 to 2005 higher than or below the baseline of their yearly resistance rates in 2000 were invalidated in cases where yearly resistance rate values for years 2001 to 2005 being used in computing average resistance rates of organisms includes percentage yearly resistant rate values considered being out of range of similar values determined for other years. In such cases inferences on increases or decreases in such organisms' resistances were made based only on deductions from trends in variations of the organisms' percentage yearly resistances as established from plots of resistance rates against years.

- **Variations in yearly resistance rates of pathogens to antibiotics**

Within the above limitations brief discussions on variations of yearly resistance rates of organisms to individual antibiotics are provided as follows.

- **Ampicillin and Penicillin**

Gram-negative bacilli *Escherichia coli, Klebsiella, Proteus* and *Pseudomonas* species exhibited high yearly resistance rates to ampicillin with demonstrations of slight increases in resistance rates to the antibiotic over the years of culture sensitivity data study. Although it may not be of importance as ampicillin and penicillin are not commonly prescribed for *Staphylococcus aureus* infections, it was deemed appropriate to report on sensitivity trends of *Staphylococcus aureus* to these antibiotics for information in view of recommendations of Lowy (2005:821) for the use of Penicillin G in treating penicillin sensitive strains of the pathogen. *Staphylococcus aureus* among the gram-positive cocci showed increasing percentage yearly resistances to ampicillin and penicillin over the

years to attain high levels of resistance of the organism against the antibiotics by the end of the culture sensitivity data study period in 2005 (Table 4.2.6; Figure 4.2.17). Lowy (2005:821) recommended the use of Penicillin G in treating Demonstrations of high resistances of GNB and *Staphylococcus aureus* are expected on account of the organisms' intrinsic production of β-lactamases or through their acquisition of extended spectrum β-lactamase (ESBL) gene bearing plasmids (Elliot *et al.*, 2004:53; Russo, 2005:882,883).

Penicillin is generally not prescribed in infections of GNB as in cases of urinary tract infections for example where these pathogens feature as most implicated aetiological agents (Sections 4.1.1.6, 4.1.2.7 and 4.1.4.3). The organisms were for this reason generally tested against penicillin a few times only, producing test results that could not be adequately analysed to realistically reflect their yearly resistance rates against the antibiotic.

As results of analysis of culture sensitivity data to establish organisms' sensitivity patterns to various formulary antibiotics showed (Section 4.2.3.1), streptococci generally demonstrated yearly resistance rates that were in conformity with their literature reported sensitivities to ampicillin and penicillin (Section 2.1.4.2). *Streptococcus pneumoniae,* isolated and identified mainly as α-haemolytic streptococci, showed low yearly resistance rates (0% - 13% for ampicillin and 12% to 38% for penicillin) that can be said to be stable within the six-years for which sensitivity data were studied with an insignificant overall decrease in its 2001 to 2005 average yearly resistance rate over its baseline resistances to the two antibiotic in year 2000. Compared with *Streptococcus pneumoniae, Streptococcus pyogenes* demonstrated higher yearly resistance rates (14% to 36% for ampicillin and 26.3% to 66.4% for penicillin) to the antibiotics. It also showed significant increases in its yearly resistance rates to the antibiotics by the last year of the data collection period. Non-haemolytic streptococci composed of enterococci and non-enterococci exhibited very significant decreasing resistances to ampicillin over the 2000 to 2005 data study [Table 4.2.6; Figure 4.2.17(a)].

Results of associations of bacterial isolates and specimens identified streptococci including *S. pneumoniae, S. pyogenes* and non-haemolytic streptococci, after *Klebsiella* spp and *Staphylococcus aureus* as most common bacterial isolates from sputum

specimens and hence their identification as leading pathogens of respiratory tract infections following *Klebsiella* spp and *Staphylococcus* (Figure 4.2.13). Similarly results of antibiotic prescription pattern study as presented in sections 4.1.1.6 and 4.1.2.7 identified ampicillin as the most and penicillin one of the most frequently prescribed antibiotics in respiratory tract infections (Tables 4.1.15 and 4.1.33). These results have established high exposure of *S. pneumoniae* and *S. pyogenes* to penicillin and ampicillin and the observed development of resistance. Increasing trends in resistance demonstrated by these pathogens to the antibiotics is postulated to be a result of this high exposure of the organisms to the antibiotics. Extensive use of antibiotics within populations as indicated in an earlier paragraph has the effect of inducing pathogen antibiotic resistance development by mechanisms of selective pressure and the high and increasing yearly resistance rates of these pathogens, particularly *S. pyogenes*, is attributable to this. The almost stable low yearly resistance rates of *S. pneumoniae* to ampicillin observed over the study period in spite of the high rate of use of the antibiotic in respiratory tract infections may be explained by the influence of other factors including the intrinsic susceptibility of the pathogen to the β-lactam antibiotics generally (Musher, 2005:811).

Non-haemolytic streptococci comprise enterococci (*E. faecalis and E. faecium*) and enterococcal streptococci. Both types of organisms differ in their sensitivity to the penicillins. Enterococci are known to be intrinsically resistant to the penicillin or ampicillin (Inglis, 2003:245; Johnson *et al.,* 2001:S8), while non-enterococcal streptococci demonstrate intrinsic sensitivity to the penicillin and ampicillin (Wessels, 2005:823). The reported decrease in percentage yearly resistance of non-haemolytic streptococci to both penicillin and ampicillin may for these reasons be indicative of more of isolations and sensitivity testing of penicillin and ampicillin resistant (enterococci) and penicillin and ampicillin sensitive (non-enterococcal streptococci) members of this classification of streptococci in different years than of non-haemolytic streptococci species with same sensitivity characteristics to both antibiotics demonstrating decreasing sensitivity to the antibiotic below high baseline resistance rates over a number of years.

- **Erythromycin**

Other GNB apart from *Escherichia coli* were also tested against erythromycin but have been disregarded on the grounds of data on frequencies of their testing for most years

being too limited to be considered valid for the determination of their yearly resistance rates for analysis to show reliable trends of variations in the yearly resistance rates of the organisms over the years of study.

The reported increasing trends in yearly resistance rates of *Escherichia coli* and *S. pneumoniae* and the overall increase in the yearly resistance rates of *Staphylococcus aureus* and *S. pyogenes* to the antibiotic [Table 4.2.8; Figure4.2.19(a)] are expectedly outcomes of high rates of use of erythromycin as reported in results of the antibiotic prescription pattern study (Sections 4.1.1.4, 4.1.2.5). Erythromycin by these results, though not much prescribed among inpatients, is the third most prescribed antibiotic after ampicillin and co-trimoxazole among outpatients for the empiric treatment of respiratory tract infections and one of the three antibiotics most prescribed in genitourinary tract infections. High rates of use of given antibiotics, as explained in earlier paragraphs, orchestrate increased rates of resistance development of pathogens to such antibiotics by mechanisms of selective pressure. The development of increasing resistance of the above pathogens which are associated with infections for which erythromycin is much used, can be attributed to the extensive prescription of the antibiotic for infections of these organisms.

Disregarding the low yearly resistance rate reported in year 2000 for non-haemolytic streptococci on the basis of too few organisms being tested for their sensitivity that year, non-haemolytic streptococci can best be described as displaying a stable yearly resistance rate to the antibiotic in the range of 30% and 35% in the six-years of the culture sensitivity data study period. This observed trend defiles expected increases in the resistances of the organisms to the antibiotic resulting from increased use of erythromycin as reported above. A most probable explanation for this could be effects of the species composition of this classification of streptococci. Non-haemolytic streptococci, as indicated in discussions on resistance trends of this group of organisms to ampicillin and penicillin, comprise both enterococci and non enterococcal streptococci that have differing sensitivity characteristics to antibiotics. For this reason, increases or decreases in resistance trends to given antibiotics over given periods as thought, would to be more apparent only if all members of the classification were to show the same trend in their resistances to the antibiotic.

- **Methicillin/ Cloxacillin**

Methicillin was tested mainly against *Staphylococcus aureus* as results indicated. The antibiotic was also tested against GNB but at very low frequencies of testing. Percentage yearly resistant values calculated for most years from such low frequencies of testing were found deficient in their reliability for use in determining trends in variations of the organisms' yearly resistance rates over the years of study and have thus been disregarded.

The reported inconsistency in the variation of yearly resistance rates of *Staphylococcus aureus* over the years of culture sensitivity data study was mainly due to an isolated high yearly resistance rate of 78% reported for the organisms in 2002. The number of isolates of the organism tested for their sensitivity against the antibiotic in that year is much lower than those of other years and should be the contributing factor to the observed deviation in trend [Table 4.2.9; Figure 4.2.19(a)].

Disregarding this reported out of range yearly resistance rate renders *Staphylococcus aureus* to be reviewed as exhibiting stability in its resistance to cloxacillin/methicillin in the range of 17.2 to 39.0% over the period of culture sensitivity data study. Results of antibiotic prescription pattern study presented in Sections 4.1.1.4 and 4.1.2.5 establishes cloxacillin as the most commonly prescribed antibiotic in *Staphylococcus aureus* associated infections. Yearly resistance rates of the organism to the antibiotic rose up to 39% and, even if stable, indicated a problem of an increase in methicillin resistant strains of the organisms in the study environment and a need to introduce more effective antibiotics at the study sites for the treatment of *Staphylococcus aureus* infections in the event of treatment failures with the antibiotic.

- **Tetracycline**

Yearly resistance rates for cocci organisms against tetracycline were seen to be generally stable over the six-years of data study period. This, however, also indicated the exception of *S. pneumoniae* for which increasing trends in yearly resistance rates to tetracycline were observed. The general trends in resistance rates of the organisms to the antibiotic over the years, were seen to drop from initial high rates in 2000 to lower stable rates in following years of the study period for *Staphylococcus aureus* and non-haemolytic streptococci or found to be stable throughout the six-year period of data study for *S. pyogenes*. Similarly, and with the exception of *Escherichia coli* for which

significant increasing trends in yearly resistance rates to tetracycline have been recorded, stability in yearly resistance rates of GNB to tetracycline have generally been described [Table 4.2.10; Figure 4.2.21(a)].

Except for their prescription in sexually transmitted disease manifesting with symptoms of penile or vaginal discharges in line with recommendations in the standard treatment guidelines of Lesotho, tetracyclines (tetracycline or doxycycline) are currently less frequently prescribed in comparison with other antibiotics in treating infections either of gram-positive or gram-negative bacteria at study site hospitals (Sections 4.1.1.4 and 4.1.2.5). Lower prescription rates of an antibiotic that had previously been prescribed at high rates among a population is known to result in reversal of resistance pathogens acquired to the antibiotic due to its over-prescribing (Gould, 1999:460). This may in theory explain the trend of yearly resistance rates to tetracycline observed for most organisms as results depict.

The observed increases in resistances of *Escherichia coli* may be linked to the high rate of use of the tetracyclines in genitourinary tract infections where the antibiotic is recorded as one of the three most frequently prescribed antibiotics in treating genitourinary tract infections (Section 4.1.2.5). The increase in resistance of the pathogen to tetracycline may in this case be explained as being caused by the extensive use of the antibiotic in treating genitourinary tract infections to which *Escherichia coli* is an associated pathogen. Increasing resistance of *S. pneumoniae* to the antibiotic may be associated with an observed increasing resistance of the pathogen to penicillin. Pneumococci susceptibility to co-trimoxazole and tetracycline is documented in literature to increase with increases in penicillin resistance of the pathogen (Inoue *et al.*, 2004:47). The observed increase in yearly resistance rates of *S. pneumoniae* to tetracycline is seen, for this reason, to reflect a parallel effect of the observed yearly increases in resistance rate of the pathogen to penicillin.

- **Co-trimoxazole**

S. pyogenes, S. *pneumoniae* and non-haemolytic streptococci showed variations in their yearly resistance rates to co-trimoxazole that exhibited as parallel decreases in yearly resistance rates from high resistance levels in year 2000 to lower levels in 2002 followed

by resumption of increasing yearly resistances for the rest of the period for which pathogen antibiotic sensitivity studies were done [Table 4.2.11; Figure 4.2.22(a)].

In the absence of any study results describing patterns of antibiotic prescribing at study sites in years preceding the study period and to account for the observed decrease in the organisms' resistances to the antibiotic from 2000 to 2002, it could only be speculated that, perhaps, there had been a fall in rates of co-trimoxazole prescribing at study sites, for whatever reason, during the period 2000 to 2002. This speculation is advanced in explanation of the observed fall in resistance of the pathogens to the antibiotic in view of Gould's (1999:460) notation of rapid reversal of pathogens' resistance to a given antibiotic if the rate of prescription of that antibiotic is reduced. In the event of a discount of such speculation, particularly in a situation as this where increasing resistances of other pathogens to the antibiotic have been noticed in the period of decreasing resistances of the streptococci, a postulate of the possibilities of streptococci losing their resistances to the antibacterial agent even in periods of high rates of its use is advanced for investigation.

The resumption of increasing resistances of streptococci, *vis a vis* reported increasing trends in yearly resistance rates over the study period of *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella* and *Pseudomonas* species is hypothesised to result from current high rates of use of the antibiotic as study results reported in Sections 4.1.1.4 and 4.1.2.5) confirmed. High rate antibiotic use, as repeatedly indicated in earlier sections of this write up is a harbinger to resistance development of organisms to antibiotics. Use of co-trimoxazole in the prophylaxis and management of opportunistic infections in HIV/AIDS is highly encouraged (Watera *et al.*, 2006:373). With current high rates of the infection in sub-Saharan Africa, Lesotho inclusive, the observed high rates of use of the antibacterial agent as reported could be a result of this drive to use the agent in the management of opportunistic infections in HIV/AIDS.

Reports of *Proteus* spp showing more stable resistance to co-trimoxazole over the period of study with a variation in percentage yearly resistance rates characterised with decreases from high (86%) to fairly high (62%) resistance levels followed by signs of increasing resistance, may be due to different individual members of the species demonstrating differing characteristics in resistance development to co-trimoxazole. The

observed decreases in yearly resistance rates in these cases may actually be a result of differing percentage compositions of individual members of the species isolated and tested for their sensitivities in a given year. *Proteus mirabilis,* for example, is considered susceptible to most antibiotics including co-trimoxazole while *Proteus vulgaris* and *Proteus penneri* on the other hand are considered more resistant and which in part explains the high yearly resistance rates to the antibiotic observed for the pathogens (Russo, 2005: 883). *P. Mirabilis,* though considered susceptible to most antibiotics can acquire resistance to antibiotics, through acquisition of extended spectrum β-lactamase (ESBL) gene bearing plasmids to explain increases in resistance of the organisms to such antibiotics at times of their over-use in treating infections. ESBL-producing strains of *Proteus mirabilis* isolates resistant to co-trimoxazole and other antibiotics have been reported in the literature (*Luzzaro et al., (2001:131*). This may explain reported increasing resistance of *Proteus* species to co-trimoxazole by the end of period of culture sensitivity results study.

- **Chloramphenicol**

Stable or decreasing trends in variations of yearly resistance rates of most organisms tested against chloramphenicol for their sensitivities have generally been seen as results of the study indicate. Specific organisms showing such trends in yearly resistance variation include non-haemolytic streptococci, the only species of streptococci tested regularly against chloramphenicol over the period of study, *Staphylococcus aureus*, *Escherichia coli, Klebsiella* spp and *Pseudomonas spp*. *Proteus* spp, apart from exhibiting decreasing trends in resistance variation for the greater part of the period of culture sensitivity studies reportedly demonstrated observed increases in resistance towards the end of the period of study [Table 4.2.13; Figure 4.2.23(a)].

Chloramphenicol by result presentations in Sections 4.1.1.4 and 4.1.2.5 is one of the least used antibiotics in treating infections in both inpatients and outpatients at study sites. Limited use of the antibiotic is indicative of an absence of resistance development by organisms to the antibiotic by mechanisms of selective pressure. Resistances of organisms to chloramphenicol that have been observed to be stable or decreasing over time could be intrinsic resistances of the indicated organisms to it or resistances acquired by the organisms through other mechanisms particularly by mechanisms of ESBL gene acquisition through inter-organism plasmid transfer. Reported decreases in

organisms' resistances to the antibiotic are suggestive of possibilities of such organisms losing their resistances to chloramphenicol over time as a result of the sparing use of the antibiotic (Gould, 1999:460). Individual members of *Proteus* species may, as explained in the case of co-trimoxazole, have differing sensitivity characteristics to chloramphenicol to make observed yearly resistances of the species to the antibiotic partly dependent on what percentage proportion of the species have been tested in a given year. The observed increasing resistances of *Proteus* spp to the antibiotic is by this reason assumed to be a result more of the resistant than the less resistant strains of the species being tested in year 2005 than being due to mechanisms attributable to any increase in the use of the antibiotic.

- **TGC (Cefotaxime/Ceftriaxone)**

By result indications activities of the third generation cephalosporins (TGCs) (cefotaxime or ceftriaxone) were tested mainly against *Staphylococcus aureus* and gram-negative bacilli (*Escherichia coli, Klebsiella, Proteus* and *Pseudomonas* spp). Generally, but uniquely, all five organisms or species of organisms were seen to demonstrate initial increasing trends in their yearly resistance rates to TGCs from the year 2000 up to the year 2003, or 2002 in the case of *Klebsiella,* followed by diminishing resistances in following years. *Staphylococcus aureus* and *Proteus* spp demonstrated resumptions of increases in their yearly resistance rates to the antibiotics towards the end of the data study period while *Escherichia coli, Klebsiella* and *Pseudomonas* spp showed no such resumptions of phases of increasing resistance following years of decreases in their yearly resistance rates to the antibiotics [Table 4.2.13; Figure 4.2.24(a)].

The unique trends in variations of such resistances by all five major organisms tested against the antibiotics as described above may be suggestive of changes in patterns of supplies of the TGCs to wards to indicate periods of high and low rate prescribing of these antibiotics among inpatients. This pattern of supply and use of the TGC in use is suggested to account for the observed increasing and decreasing phases of resistance development of organisms to the antibiotic. The suggestion is in accordance with explanations of the mechanisms of organisms' resistance development to an antibiotic within a population by selective pressure (Colgan & Powers, 2001:999) or reversal of such resistances if the rate of prescribing of the antibiotic in question is reduced (Gould, 1999:460). However, in absence of relevant information on consumption patterns of the

TGCs, reasons of the antibiotics' rate of prescribing as causes of the observed increasing and decreasing trends in organisms' yearly resistance rates to the antibiotics cannot be substantiated and hence provided as valid explanations for variations in resistance trends as observed.

The effect of multiple resistance development of organisms to antibiotics emanating from transmission of resistance development properties from one organism to another is to some extent seen as offering an acceptable explanation to the parallel increases and decreases of organisms' demonstrated yearly resistance rates to the TGCs. *Staphylococcus aureus* strains resistant to semi-synthetic penicillin resistant penicillins like methicillin or cloxacillin, are resistant not only to the penicillins but also to many other antibiotic families, including the cephalosporins (Lowy, 2005:821). Also, and as further indicated by Jones *et al.* (2003:408), the majority of methicillin resistant *Staphylococcus aureus* have been seen to cross resistance to other antibiotics including amoxycillin/clavulanate, and the TGCs while methicillin susceptible *Staphylococcus aureus* (MSSA) and methicillin susceptible coagulase-negative staphylococci (MS-CNS) are also seen to be susceptible to the TGCs. For this reason of *Staphylococcus aureus* crossing its antibiotic resistance development properties to other pathogens, parallel increases and decreases of organisms' resistances to the TGCs, as results of this study show, may be originated by similar antibiotic resistance characteristic properties acquired by other pathogens from *Staphylococcus aureus.* The semi-synthetic penicillin resistant penicillin, cloxacillin is prescribed empirically against all infections for which *Staphylococcus aureus* is suspected as an aetiological agent, making the antibiotic one of the most frequently used antibiotics in hospitals in Lesotho (Sections 4.4.1.4 & 4.1.2.5). Whatever effects this may have on the resistance patterns of *Staphylococcus aureus* could be transmitted to other organisms as well. By explanations provided above, this could have direct bearings on organisms' sensitivity patterns to the TGCs and other antibiotics. Periods of increasing resistances of organisms to the TGCs by these reasons most probably reflects effects of cloxacillin over-prescribing among the population. Years reported to have shown decreases in resistances of the organisms may actually be years where isolates of organisms tested against the TGCs might be more of methicillin susceptible strains of *Staphylococcus aureus* than methicillin resistant strains of the organism.

According to information provided by the Principal Laboratory Technician at the Queen II hospital, Mbo-Budiaki (2010), TGCs are reserved for the treatment of GNB infections

and are hence not regularly tested against streptococci in spite of its known use in the treatment of pneumocccocal infections Musher (2005:813). This explains the lack of CST results data for analysis to determine sensitivity trends of streptococci against the antibiotics.

- **Gentamicin and Amikacin**

Within provisions of assumptions made to disregard yearly sensitivity determinations found to be out of range of those of other years of the study period all organisms tested regularly against the aminoglycosides including *Staphylococcus aureus* and the gram-negative bacilli (*Escherichia coli*, *Proteus*, *Klebsiella* and *Pseudomonas* spp), reportedly demonstrated stable yearly resistance rates to this class of antibiotics within narrow ranges of percentage yearly resistance variations. This is with the exception of non-haemolytic streptococci (enterococci and non-enterococcal streptococci), the only streptococci tested against the antibiotic, which exhibited increasing trends in their percentage yearly resistance to gentamicin [Figure 4.2.25(a)].

While seen to exhibit less variation in their resistance to these antibiotics, organisms generally were seen to display higher levels of resistance towards gentamicin than amikacin. *Staphylococcus aureus* displayed resistance rates of between 25.0% and 42.0% to gentamicin as compared to its percentage yearly resistance range of 0.0% to 21.0% for amikacin; *Escherichia coli* 11.0% to 18.0% for gentamicin as compared with 0.0% to 13.0% for amikacin; *Klebsiella* spp 13.0% to 39.0% for gentamicin in comparison with 0.0% to 13.0% for amikacin; *Proteus* spp 10.0% to 30.0% for gentamicin in comparison with 0.0 to 30.0% for amikacin and *Pseudomonas* 12.0% to 20% for gentamicin as compared to 0.0% to 8.0% for amikacin [Table 4.2.14 & 4.2.15; Figures 4.2.26(a)].

Gentamicin by result indications of section 4.1.1.4 is the most frequently and amikacin the least frequently prescribed antibiotic among inpatients at study sites. Differences in individual intrinsic activities of either gentamicin or amikacin still withstanding, the high rate of use of the former aminoglycoside may partly account for the higher levels of resistance shown by organisms to it than the latter. The results place amikacin as a second choice antibiotic that could be used in treating infections following treatment failures with gentamicin if culture sensitivity tests do not negate such usage in the events

of the two antibiotics exhibiting cross resistance in their actions towards infecting pathogens.

The literature reports non-haemolytic streptococci, *Enterococci faecium* and *Enterococci faecalis* as having intrinsic resistance to the aminoglycosides (Johnson *et al.* 2001:S7). Selection of such strains for growth in the face of an over-use of an antibiotic that eradicates susceptible strains may result in increases in resistance development. Gentamicin having been established as the most frequently prescribed parenteral antibiotic among inpatients as reported above may have selected strains of *E. faecium* and *E. faecalis* for growth to account for the observed increasing resistance of the non-haemolytic streptococci to the antibiotic during the culture sensitivity data study period.

The stability demonstrated by all organisms in their resistance to the aminoglycosides defiles theoretical expectations manifesting as increasing yearly resistance rates of organisms to gentamicin emanating from mechanisms of bacterial pathogen antibiotic resistance development by selective pressure due to the reported high rates of gentamicin prescribing among inpatients (Section 4.1.1.4). In the review of the literature many studies reported increases of organisms' resistances to the aminoglycosides attributable to a high rate of utilisation of the class of antibiotics in the treatment of infections in localities where the studies were done. Examples of such studies included the Lari *et al.* (1998:637) study which documented resistances of *Pseudomonas* spp to gentamicin and amikacin to be as high as 95.0% and 49% at the Tohid Burn centre in 1995 and with resistance of amikacin further increasing up to 90% by 1997 due to the intensive use of antibiotics in these areas. Ariffin *et al.* (1999:24) also reported increases in the resistance of *Klebsiella pneumoniae* to amikacin from 21% in 1990 to 54% in 1997 due to the empiric prescription of this antibiotic at the oncology units of their study hospital. Similar reports also showed increases in resistance of *Proteus* and *Klebsiella* spp to the aminoglycosides due to multi-drug resistant effects mediated by plasmid containing ESBLs genes which also have been linked with resistance determinants for aminoglycosides (Luzzaro *et al.* 2001:131; Russo, 2005:880). These studies confirm as in the cases of many other antibiotics, that organisms do develop increases in their resistance to the aminoglycosides by mechanisms emanating from either a high rate use of the antibiotics or multi-drug resistance development from resistance development mechanisms akin to other antibiotics.

The observation of all gram-negative bacilli (*Escherichia coli*, *Proteus*, *Klebsiella* and *Pseudomonas* spp) and *Staphylococcus aureus* demonstrating the same trend in the variations of their yearly resistance to the antibiotics suggests interplay of factors in the use of antibiotics at study site hospitals that kept the development of resistances of these organisms to the aminoglycosides at bay. A postulate which could be advanced to explain this observation if proved to be true may have to do with other antibiotics prescribed with it in multiple therapies. Results presentations in Section 4.1.1.3 established 55.7% of all inpatient antibiotic prescriptions as being composed of two (2) or more antibiotics and as many as 22.85% being composed of three or more antibiotics. With this high rate of multiple antibiotic therapy in wards, gentamicin is most likely to be prescribed with other antibiotics rather than being prescribed as a mono-therapy. Multiple empiric antibiotic therapy, despite being associated with lack of rationality in prescribers' judicious selection of antibiotics (Chambers, 2001:1169), may have higher chances of eradicating pathogens before they could develop resistance to one of the antibiotics in the multiple therapy. This particularly may be the case if prescribed antibiotics in the multiple therapy have different mechanisms of actions and may be synergistic in their activity against the infecting pathogen(s). Wilton *et al.* (2002:114) gave credence to this statement when they indicated that antibiotic combinations may work through preventing sensitive organisms from becoming drug resistant during treatment. Dubberke (2005:1), in explaining the mechanism of suppression of drug resistance development by multiple antibiotic therapy said such therapies cause decrease in the emergence of resistance through an increase in the number of genetic elements necessary to express resistance. The author cited the case of multiple antibiotic use in the treatment of tuberculosis to support his opinion.

In order to explain the observed lack of increase in resistance development of organisms to gentamicin despite its high rate of prescribing in inpatient settings at study sites, two postulates are put forward. The first of these is the postulate that other antibiotics with which gentamicin is prescribed most of the time in multiple antibiotic therapies may be synergistic with its mechanism of action in a way as to exercise an impact on it more efficiently in its eradication of pathogens before they could develop resistance to it. Gentamicin (as well as other aminoglycosides) is known for example to be synergistic with β-lactam antibiotics (Musher, 2005:813; Sabella & Goldfarb, 1999:3) and is prescribed together with these antibiotics most often in the wards. It is possible that

combined therapies of gentamicin and the penicillins as prescribed together in inpatient settings may actually be accountable for the efficient killing of pathogens before they could develop resistance to gentamicin.

- **Ciprofloxacin**

Calculated yearly resistant rates of organisms to ciprofloxacin varied erratically over the years with no specific established trends showing either increases or decreases in yearly resistance rates of most organisms to the antibiotic. This is attributable to the inconsistency with which laboratories tested pathogens against the antibiotic and which has been indicated as a limitation of the study.

Within provisions of assumptions made to justify non-consideration of percentage yearly resistances out of range of determinations for other years, plots of yearly resistance rates against years of such determinations still showed variations in pathogens' yearly resistance rates that have not shown distinctive trends describable as increasing, decreasing or stable and results as provided can be regarded only as the best descriptive analysis that could be given in the circumstances [Table 4.2.15; Figure4.2.27(a)].

It is difficult to provide tangible explanations to the observed trends in variations of yearly resistance rates of organisms to the antibiotic based on known theories of mechanisms of bacteria antibiotic resistance development. The antibiotic by results of Sections 4.1.1.4 and 4.1.2.5, is not much used as a regular and empirically prescribed antibiotic among inpatients. Its prescribing among outpatients is also at a low rate compared to other antibiotics and is limited mainly to genitourinary tract infections manifesting with penile or vaginal discharges for which its prescribing is recommended in the standard treatment guidelines (Ministry of Health & Social Welfare, 2006: 65 & 66). Taking into account the effects of high rate use of antibiotics as promoting the development of pathogen resistance to such antibiotics as indicated in earlier paragraphs, such low rate use of the antibiotic is considered conducive to the retention of antibacterial activity of the antibiotic and explains generally the low percentage yearly resistance rates demonstrated by various organisms to it.

Methicillin sensitive *Staphylococcus aureus* (MSSA) as indicated in the literature has low resistance rates of between 4.5 to 12% to ciprofloxacin and many other antibiotics

(Jones *et al.* 2003:408) while about 16.7% of methicillin resistant strains of the organisms (MRSA) were also seen to be resistant to the antibiotic according to Brown and Ngeno (2007:223). Further documentations in the literature indicated MRSAs to be characteristically resistant to all other semisynthetic penicillinase resistant penicillins (SPRPs) and other antibiotics inclusive of the quinolones (Lowy, 2005:82). From such literature derived information, the *Staphylococcus aureus'* sensitivity pattern to the ciprofloxacin showing up to 32% yearly rates of resistance of the organism to the antibiotic can be taken as indicating the presence of both MSSA and MRSA strains of the organism at study site hospitals, with each of these having chances of being isolated depending on whether they are the causative agents of the infection for which specimens are taken. The observed decreased percentage yearly resistances in *Staphylococcus aureus* to ciprofloxacin over the years for this reason may rather be attributable to higher percentage fractions of isolates of MSSA being isolated and tested for their sensitivities in those years than any probable decreases in resistance properties of MRSA strains to the antibiotic.

MRSA strains are not only resistant to other antibiotics as indicated but are also capable of passing genetic materials to other organisms to confer such resistance properties on them. *Escherichia coli*, *Klebsiella* and *Proteus* spp do easily acquire such plasmid bearing genes to code for ESBLs and become resistant to other antibiotics including ciprofloxacin. *Klebsiella* spp in particular is known to have a high propensity to developing multi-drug resistant strains through acquisition of plasmid containing genes encoding for ESBLs and up to about 50% ESBL containing strains of the pathogen have been seen to display associated resistance to fluoroquinolones (Russo, 2005:883). Obvious implications of these are the existences of strains of these organisms that may be resistant or not resistant to the antibacterial effects of ciprofloxacin. The resistance variation patterns they show towards the antibiotic would, as explained for *Staphylococcus aureus* partly depend on which isolates of these strains, either resistant or susceptible, had been tested against the antibiotic at any one time.

Some studies like that of Blandino *et al.* (2004:516) showed *P. aeruginosa* strains to be resistant up to levels of about 54.6% to ciprofloxacin. This finding suggests, as in the case of other organisms, the possibility of *Pseudomonas* developing by whatever mechanism an appreciable resistance to the antibiotic. The reported low levels of

resistance of *Pseudomonas* to the antibiotic are indicative of lack of such fluoroquinolone resistant strains of the organism in patient groups. This in theory can be associated with the seemingly low rate of use of the antibiotic as results presentations of antibiotic prescription pattern studies showed (Sections 4.1.1.4 & 4.1.2.5).

The decreasing trends in resistance of most of organisms which in themselves indicated higher chances of isolating their susceptible strains to the antibiotic, suggest rather lower percentage proportions of resistant strains of the organisms among patient populations. In spite of a lack of well-defined trends in variations of pathogen percentage yearly resistance to allow for easy interpretations in resistance variation curves of organisms over the years, it is clearly obvious from the above considerations that ciprofloxacin has appreciably retained its efficacy due to its low rate of use and can continue to be effectively used in infections of GNB except in infections of *Klebsiella* which on the average showed high resistance rates to the antibiotic.

- **Nalidixic acid and Nitrofurantoin**

Nalidixic acid and nitrofurantoin by results presentations in Sections 4.1.2.5 are prescribed primarily for urinary tract infections uncomplicated with penile or vaginal discharges and tests on their activities against organisms are carried out more routinely against *Staphylococcus aureus*, and gram-negative bacilli, namely, *Escherichia coli*, *Klebsiella*, *Proteus* and *Pseudomonas* spp.

Number of times *Proteus* and *Pseudomonas* spp were tested against the nalidixic acid and nitrofurantoin in most years of the study period were too few for calculated percentage yearly resistances using their low frequencies of testing to be analysed to give meaningful trends in their yearly resistance rate variation for interpretation to show whether there had been increases or decreases in their resistances to the antibiotics over years of the study period. On assumptions, however, that such limited numbers of the pathogens isolated and tested have higher chances of being isolated on account of their higher presence in the population, yearly resistance rates of the organisms as determined from such low frequencies of isolation can be interpreted as providing a clue to their resistance patterns to the given antibiotics. On this basis and by result presentations in Tables 4.2.17 & 4.2.18 *Proteus* and *Pseudomonas* spp can be said to have high rates of resistance to nalidixic acid and nitrofurantoin. Disregarding on the

basis of their being out of range of yearly resistance determinations for other years, percentage yearly resistances of 100% and 0.0% determined from the 1 (one) isolate each of the two organisms tested in year 2005 against nitrofurantoin, or 0.0% resistance rate determined for 3 (three) isolates of *Proteus* tested in year 2000 against nalidixic acid, *Proteus* spp can be seen as showing resistance rates to the two antibiotics that ranged between 33.0% and 50.0% for nalidixic acid and 39.0% and 85% for nitrofurantoin over the years while *Pseudomonas* spp similarly exhibited variations in resistance rates of between 33.0% to 50% resistance to nalidixic acid and 50% to 80% to nitrofurantoin over the years.

Result presentations above showed *Staphylococcus aureus, Escherichia coli, and Klebsiella* spp exhibiting on the average stability in their percentage yearly resistances to nalidixic acid over the years, with *Staphylococcus aureus* showing high yearly resistance rates in the range of 50% to 73% against the antibiotic while *Escherichia coli, and Klebsiella* spp respectively demonstrated variations in their yearly resistance rates within lower ranges of 14.0% to 32.0% against the antibiotic over the years of study.

Escherichia coli and *Klebsiella* spp were seen to display yearly resistance rates to nitrofurantoin that also showed stable variations over the years of study and within ranges of between 9.0% and 20% for *Escherichia coli* and 18.0% and 39% for *Klebsiella* spp. *Staphylococcus aureus* showed an erratic variation in its percentage yearly resistance to nitrofurantoin which on the average varied between 0.0% and 40.0% [Table 4.2.17; Figure 4.2.29(a)].

Though identified as antibiotics used primarily in uncomplicated urinary tract infections their rates of prescribing generally are low as results presentations in Section 4.1.2.5 show and may not evoke mechanisms of organisms' resistance development by selective pressure as seen generally in situations of extensive prescribing of antibiotics within populations. This largely explains the observed stability in observed percentage yearly resistances of organisms to the antibiotic. The display of high yearly resistance rates of some pathogens to the antibiotics as seen with *Staphylococcus aureus,* for example, more appropriately could be attributed to other mechanisms like those of multi-drug resistant development by processes of organisms' acquisition of ESBL gene bearing plasmids.

4.2.4. Antibiotic selection for empiric treatment of infections: Practical use of percentage overall activity (POA) and antibiotic selection factors (ASF) in the selection of antibiotics

The section presents results of using an innovative procedure in selecting antibiotics in the empiric treatment of infection types reportedly seen at study sites and for which bacteria pathogens associated with their causes have been investigated and reported in Section 4.2.2. The procedure involved the use of a number of formulae derived from first principles in determining antibiotics that are most active among a group of other antibiotics considered against the most common pathogens associated with the infections and which at the same time produce treatment costs considered most affordable to the patient or at least cost to the health institution. The results as presented illustrate the practical use of the formulae. Though actual antibiotic sensitivity patterns of pathogens identified by this study (Section 4.2.2) had been used in the determination results produced may not be taken as authentic in view of limitations cited for Phase II of this study. Discussion on the section is extended beyond evaluations of the results to include discussions on the rationale behind the derivation of the formula as presented in Chapter 3 and explanations of other factors that need to be considered in antibiotic selection processes adopting the procedure.

4.2.4.1 Results

Table 4.2.19 summarises results of antibiotics selected for empiric treatment of various infections for which specimens sent to study site microbiology laboratories were investigated for their microbial components and sensitivities of isolated pathogens to formulary antibiotics.

On the basis of cefotaxime being available only in parenteral formulation its selection in preference to other antibiotics based on its "antibiotic selection factor" (ASF) values may be considered only when it is to be given as a single dose to effect a cure as recommended for example in the treatment of gonorrhoea (Ram & Rice, 2005:861) as cost of dose indicated for it is based on a one-day treatment course. In situations where it is to be used for a number of days its selection above other antibiotics can be based only on its "antibiotic treatment success to failure ratio" (ATSFR) or "percentage overall activity" (POA) values. With these notations and based on values of their calculated

ATSFRs and ASFs the following antibiotics are selected in order of their advantages in respect to their expected treatment outcomes and costs in treating indicated infections.

- **Ascites complicated with primary or spontaneous bacterial peritonitis**:
  - Based on ATSFR
    - Ciprofloxacin, Cefotaxime, Chloramphenicol, Tetracycline
  - Based on ASF
    - Ciprofloxacin, Tetracycline, Chloramphenicol, Cefotaxime

- **Meningitis**
  - Based on ATSFR
    - Ciprofloxacin, Cefotaxime, Chloramphenicol, Ampicillin
  - Based on ASF
    - Chloramphenicol, Ciprofloxacin, Ampicillin, Cefotaxime

- **Lower respiratory tract infections with pleural infusion**
  - Based on ATSFR
    - Ciprofloxacin, Cefotaxime, Chloramphenicol, Ampicillin or Tetracycline
  - Based on ASF
    - Ciprofloxacin, Tetracycline, Chloramphenicol, Ampicillin

- **Lower respiratory tract infections without pleural infusion**:
  - Based on ATSFR
    - Ciprofloxacin, Cefotaxime, Chloramphenicol, Ampicillin
  - Based on ASF
    - Ciprofloxacin, Chloramphenicol, Ampicillin, Cefotaxime

Table: 4.2.19 Antibiotic selection in the empiric treatment of infections based on antibiotic activity and cost considerations

Specimen	Associated Clinical Infections	Commonly associated bacteria (Lesotho)	Antibiotic selection determining factors						Selected antibiotics	
			Antibiotics	POA	POR	ATSFR	Antibiotic cost per COT (Rands)	ASF	ATSFR considered	ASF considered
Ascitic fluid	Ascites complicated with Primary or spontaneous bacterial peritonitis,	*S. pneumoniae)* *S. aureus* *Escherichia coli* *Klebsiella spp*	Ciprofloxacin	76	24	3.2	8.50	0.38	Ciprofloxacin	Ciprofloxacin
			Cefotaxime Injection	74	26	2.8	17.80*	0.16	Cefotaxime Injection	Tetracycline
			Chloramphenicol	60	40	1.5	4.48	0.33	Chloramphenicol	Chloramphenicol
			Tetracycline	42	58	0.7	1.96	0.35	Tetracycline	Cefotaxime Inj*
Cerebrospinal fluid	Meningitis	*S. pneumoniae)* Non-Haem strep *S. aureus* *S. epidermidis* Neisseria spp *Escherichia coli* *Klebsiella spp* *Haemophilus influenzae*	Ciprofloxacin	84	16	5.3	8.50	0.62	Ciprofloxacin	Chloramphenicol
			Cefotaxime Injection	78	22	3.5	17.80	0.20	Cefotaxime Injection	Ciprofloxacin
			Chloramphenicol	77	23	3.3	4.48	0.74	Chloramphenicol	Cefotaxime Inj
			Ampicillin	69	31	2.2	11.80	0.19	Ampicillin	Ampicillin
Pleural fluid	Respiratory infections	*(S. pneumoniae)* Non-Haemolytic streptococci *S. aureus* *Klebsiella spp*	Ciprofloxacin	78	22	3.5	8.50	0.41	Ciprofloxacin	Tetracycline
			Cefotaxime Injection	75	25	3.0	17.80*	0.17	Cefotaxime Injection	Chloramphenicol
			Chloramphenicol	69	31	2.2	4.48	0.49	Chloramphenicol	Ciprofloxacin
			Ampicillin	51	49	1.0	11.80	0.08	Ampicillin	Cefotaxime inj
			Tetracycline	51	49	1.0	1.96	0.51	Tetracycline	Ampicillin

Specimen	Associated Clinical Infections	Commonly associated bacteria (Lesotho)	Antibiotic selection determining factors						Selected antibiotics	
			Antibiotics	POA	POR	ATSFR	Antibiotic cost per COT (Rands)	ASF	ATSFR considered	ASF considered
Ear swab	Ear infections	*S. pneumoniae)* *S. pyogenes*) Non-Haem strep *S.aureus* *S. epidermidis*	Ciprofloxacin	83	17	4.9	8.50	0.58	Ciprofloxacin	Ciprofloxacin
			Cefotaxime Injection	80	20	4.0	17.80*	0.22	Cefotaxime Injection	Tetracycline
			Chloramphenicol	57	43	1.3	4.48	0.15	Chloramphenicol	Chloramphenicol
			Tetracycline	37	63	0.6	1.96	0.31	Tetracycline	Cefotaxime Injection
Throat Swab	Bacterial infections of upper respiratory structures	*S. pneumoniae)* *S. pyogenes*) Non-Haem strep *S. aureus*	Ciprofloxacin	89	11	8.1	8.50	0.95	Ciprofloxacin	Ciprofloxacin
			Cefotaxime Injection	81	19	7.4	17.80*	0.42	Cefotaxime Injection	Cefotaxime Inj*
			Ampicillin	71	29	2.4	11.80	0.20	Ampicillin	Chloramphenicol
			Chloramphenicol	67	39	1.7	4.48	0.38	Chloramphenicol	Ampicillin
Pus swab	Wound infections	*S. pneumoniae* *S. pyogenes* Non-Haem strep *S. aureus* *S. epidermidis* *Acinetobacter spp* *Escherichia coli* *Klebsiella spp* *Proteus* spp *Pseudomonas* spp	Ciprofloxacin	81	19	4.3	8.50	0.50	Ciprofloxacin	Ciprofloxacin
			Cefotaxime Injection	78	22	3.5	17.80*	0.20	Cefotaxime Injection	Tetracycline
			Chloramphenicol	57	43	1.3	4.48	0.29	Chloramphenicol	Chloramphenicol
			Tetracycline	38	62	0.6	1.96	0.31	Tetracycline	Cefotaxime Inj*
Sputum	Lower Respiratory	*S. pneumoniae* *S. pyogenes*)	Ciprofloxacin	85	15	5.7	8.50	0.7	Ciprofloxacin	Ciprofloxacin

Specimen	Associated Clinical Infections	Commonly associated bacteria (Lesotho)	Antibiotic selection determining factors					Selected antibiotics	
			Antibiotics	POA	POR	ATSFR	Antibiotic cost per COT (Rands)	ASF	ATSFR considered	ASF considered
	tract infections	Non-Haem strep *S. aureus* *S. epidermidis* *Klebsiella spp*	Cefotaxime Injection	72	28	2.6	17.80	0.15	Cefotaxime Injection	Chloramphenicol
			Chloramphenicol	66	33	2.0	4.48	0.45	Chloramphenicol	Cefotaxime
			Ampicillin	54	46	1.2	11.80	0.1	Ampicillin	Ampicillin
Urine	Urinary tract infections	*S. pyogenes*) Non-Haem strep *Escherichia coli* *Klebsiella spp* *Proteus* spp *Pseudomonas* spp	Cefotaxime Injection	93	7	13.3	17.80*	0.75	Cefotaxime Injection	Ciprofloxacin
			Ciprofloxacin	90	10	9	8.50	1.1	Ciprofloxacin	Chloramphenicol
			Chloramphenicol	60	40	1.5	4.48	0.33	Chloramphenicol	Tetracycline
			Tetracycline	35	65	0.5	1.96	0.26	Tetracycline	Cefotaxime Injection
High vaginal swab /Penile discharge swab	Urinary tract infections complicated with penile or vaginal discharges	*S. pneumoniae* *S. pyogenes*) Non-Haem strep *S. aureus* *S epidermidis* *Neisseria spp* *Escherichia coli* *Klebsiella spp* *Proteus* spp	Ciprofloxacin	78	22	3.5	8.50	0.41	Ciprofloxacin	Ciprofloxacin
			Cefotaxime Injection	74	26	2.8	17.80*	0.16	Cefotaxime Injection	Tetracycline
			Chloramphenicol	61	39	1.6	4.48	0.36	Chloramphenicol	Chloramphenicol
			Tetracycline	43	57	0.75	1.96	0.38	Tetracycline	Cefotaxime Injection

ABREVIATIONS: ASF: Antibiotic selection factor; ATSFR: Antibiotic treatment success to failure ratio
POA: Percentage overall activity POR: Percentage overall resistance
COT: Course of treatment

Formulae for calculations: POA: Derived from basic principles (See Chapter 3: Section 3.5)
POR = 100 - POA (See Chapter 3: Section 3.5)
ATSFR: = POA/POR
ASF: = ATSFR/Antibiotic cost per COT

* One day course of treatment only considered. Selection on ASF basis may be done only if compared with other parenteral preparations

- **Ear infections:**
  - Based on ATSFR
    - Ciprofloxacin, Cefotaxime, Chloramphenicol, Tetracycline
  - Based on ASF
    - Ciprofloxacin, Tetracycline, Chloramphenicol, Cefotaxime

- **Bacterial infections of upper respiratory structures (Throat infections):**
  - Based on ATSFR
    - Ciprofloxacin, Cefotaxime, Ampicillin, Chloramphenicol
  - Based on ASF
  - Ciprofloxacin, Chloramphenicol, Ampicillin, Cefotaxime

- **Wound infections:**
  - Based on ATSFR
    - Ciprofloxacin, Cefotaxime, Chloramphenicol, Tetracycline
  - Based on ASF
    - Ciprofloxacin, Tetracycline, Chloramphenicol, Cefotaxime

- **Urinary tract infections uncomplicated with penile or vaginal discharges:**
  - Based on ATSFR
    - Cefotaxime, Ciprofloxacin, Chloramphenicol, Tetracycline
  - Based on ASF
    - Ciprofloxacin, Chloramphenicol, Tetracycline, Cefotaxime

- **Urinary tract infections complicated with penile or vaginal discharges:**
  - Based on ATSFR
    - Ciprofloxacin, Cefotaxime, Chloramphenicol, Tetracycline
  - Based on ASF
    - Ciprofloxacin, Tetracycline, Chloramphenicol, Cefotaxime

4.2.4.2 Results Evaluation and Discussion

- **Antibiotic selection procedure development : The need**

One of the specific objectives of this study has the purpose of developing an applicable procedure for a rational selection of antibiotics in the empiric treatment of infections (Section 1.3.2). Results of empiric research Phase I indicate that nearly all prescriptions for infections were empirically prescribed and that a majority of such prescriptions involve the prescription of one (1) antibiotic in outpatient settings and more than one (>1) antibiotic in inpatient settings (Sections 4.1.1.3 and 4.1.2.4). The prescription of one antibiotic may have the therapeutic disadvantage of being ineffective if pathogens implicated in the infection are not sensitive to that single prescribed antibiotic. Empiric prescribing of more than one antibiotic in treating infections may in circumstances in which a single prescribed antibiotic may not cover all implicating pathogens, have the therapeutic advantage of having higher chances of covering more pathogens implicated in the infection as results of Section 4.1.1.5 indicated. This said though, the negative bearing on costs of such antibiotic treatment in terms of some such empirically prescribed antibiotics for the infection in question not being active against any of the pathogens implicated in the infection, disadvantages from economic perspective the prescribing of multiple antibiotic in treating infections.

Multiple empiric antibiotic prescribing if done injudiciously leads to misuse and over-use of antibiotics with its resultant orchestration for the development of resistant strains of certain pathogens against certain antibiotics (Colgan & Powers, 2001: 999; Hooton 2000:1089). Viewed in light of these, the development of a simple means of rationally selecting antibiotics with maximum or appreciable therapeutic effect at minimum monetary costs to patients and institutions in the empiric treatment of infections is deemed necessary. It is considered a major contribution of this study, particularly in resource limited countries, in to seek ways out of the dilemma of selecting and prescribing antibiotics empirically in a given infection. In the opinion of the researcher, antibiotic selection based on results of cost-effectiveness analysis studies of antibiotics commonly used in treating infections is considered beyond the reach of health institutions of resource limited countries on the basis of costs of and lack of expertise in conducting such studies.

- **Methods of procedure development**

Formulae for determining percentage overall activity (POA), antibiotic success to failure ratio (ATSFR) and antibiotic selection factor (ASF) of antibiotics based on sensitivities of bacterial isolates associated with given infections and costs of antibiotics were developed (Section 3.5) for use by prescribers in health institutions in the appropriate selection of antibiotics from within available stocks of formulary antibiotics that could produce best treatment results at affordable costs to hospitals and patients.

Logical reasoning and mathematical steps used in developing the formulae are as outlined in Section 3.3.4. The developed formula for determining POA favourably compares with similar formula developed by Blondeau and Tillotson (1999:146). These researchers developed a similar formula for determining POAs of antibiotics to help select rational antimicrobial therapy using aetiological and antimicrobial sensitivity data. The researchers did not state the fundamental principles of developing their formula for determining an activity factor (F) they used in POA determinations of antibiotics against bacterial isolates from specimens. The observation, however, that their formula compares favourably with the formula developed for determining POA of an antibiotic against possible pathogens in a specimen for this research suggests fundamental probability considerations as employed in developing formula determining POAs for antibiotics in this study (Section 3.51).

The researcher's search of the literature yielded one report of a study in which Blondeau and Tillotson (1999:146) determined POAs of antibiotics and suggested their use in selecting antibiotics in the empiric treatment of infections. Though they may be more apart from this study, the researchers' search of the literature yielded no other reports regarding the development of parameters that quantified mathematically, characteristics of antibiotics for use in the selection of the agents in the empiric therapy of infections. In effect, no comparison of results obtained for this aspect of the study was made with results of other such studies to authenticate the developed process of antibiotic selections. This said, however, Professor Derendorf (2010) (Distinguished Professor and Chairman of Pharmaceutics, University of Florida) stated this in a personal communication with the researcher as his impression on the validity of methods used in deriving the formulae and procedures of the antibiotic selection process. He wrote, "The author considered the probability of pathogens encounter, the probability of treatment

success and a cost selection factor as parameters to determine the selection of antibiotics" and that ""mathematically, the use of probability is reasonable here". Very significantly, however, he recommended validation of the model prediction using real clinical data to allow for its interpretation with respect to its benefits in fighting infections. Professor Gulig (2010), on his part and in a similar communication with the researcher, commented about the weight given to cost of antibiotics in the formula. Cost as used in the determinations was treated as a linear function as he noted. This, according to him, has the negative effect of unduly diminishing the value of ASF, the quantified characteristic of the antibiotic used in selecting preferred antibiotics that has a cost component. He noted further that in instances where antibiotics from which selections are made are relatively cheap their costs may be considered basically the same and other factors then will count most in the selection process. In clinical environments as exemplified by the case of Lesotho, where lower cost traditional antibiotics are dominantly used, this may actually be the case. In these clinical environments other factors, like percentage overall activities of antibiotics as determined in this study, may take prominence over costs in antibiotic selections. Cost of courses of antibiotics most frequently used in Lesotho, as determined from costs of antibiotics at the time of data collection for this study (Appendix 13), lie between 1.20 – 11.20 rands or the approximate equivalent of 0.16 – 1.5 US dollars.

The logic and mathematical reasoning used in these determinations with the positive result of the review of Derendorf (2010) on their correctness as indicated, are considered authentic. Calculated ASFs from these formulae are hence considered as valid characteristics which, pending the validation of therapeutic benefits of the use of this procedure in antibiotic selection using actual clinical data, can be used in practice to select antibiotics rationally for the treatment of infections.

- **Procedures and limits of use of determined characteristics in antibiotic selection**

For the practical use of POAs or ATSFRs and ASFs in the rational selection of antibiotics the following procedures and comments provided must respectively be followed or taken into consideration:

- An antibiotic with the highest ASF among a group of antibiotics that, by culture sensitivity results, are all active towards bacterial isolate(s) in a given specimen, should be selected for prescribing in favour of those with lower ASFs.

- Only antibiotics selected on the basis of their POAs or ATSFRs should be considered for selection based on their ASFs which introduce cost factors into the selection procedure.
- An antibiotic with a higher POA or ATSFR or ASF may not necessarily be selected preferentially over one with lower values of these parameters if other factors considered in the therapeutic use of the antibiotic with the higher POA, ATSRF or ASF disadvantaged its use in the patient. This study from results obtained, listed antibiotics of choice in the empiric treatment of indicated infections based foremost on their POA or ATSFR values according to procedures proposed in the selection process. These parameters fundamentally determine the chances of selected antibiotics to treat successfully indicated infections based on their activities against pathogens most likely implicated in the infections. ASF considerations become important particularly, when antibiotics being considered have competitive POAs or ATSFRs. The order of listing antibiotics to be preferably prescribed as shown in the results, is taken only as providing a needed guideline as to which of the antibiotics considered in the selection process would most successfully treat the infection, other factors being equal. The final decision on which antibiotic is to be prescribed in preference to others must equally take into consideration factors that need to be considered in the therapeutic uses of the antibiotics. These include, for example, the antibiotics' side-effects and toxicities (Gugliemo, 2008:56-14), their physicochemical and pharmacokinetic properties including their clearances and the extent of binding to proteins. The antibiotics' physicochemical properties and the extent of their binding to proteins may affect their ability to penetrate and concentrate at sites of infection (Gugliemo, 2008:56-22). The importance of clearance as a characteristic of the antibiotic to be considered in the selection process is cited in view of World Health Organizations' emphasis on a prescriber to select the best possible antibiotics that have optimal durations of actions to prevent the emergence of resistant strains of the infecting pathogens (Zafar *et al.* 2008:9). Other factors like concomitant disease states may also have to be considered in the selection process. Older patients with hearing deficits are poor candidates for potentially ototoxic aminoglycoside therapy while patients with a pre-existing seizure therapy may not have to be given imipenem if less toxic therapy can be used (Gugliemo, 2008:56-14). On the same note, antibiotics with certain known characteristics that preclude their use in certain infections may not be considered in the selection

process for first choice prescribing even if their ASF or ATSRF values are higher than those of other antibiotics from which the selection is being made. The case of ciprofloxacin is worth considering here as an example. The antibiotic demonstrated higher ASF and ATSRF values than other antibiotics considered for selection in treating lower respiration tract infections (Table 4.2.19). On account of its noted moderate activity against gram-positive cocci and for its preclusion in the empiric treatment of pneumococcal pneumonia (British Medical Association and Royal Pharmaceutical Society of Great Britain, 2003:294), it may not be used as a first choice antibiotic in the empiric treatment of this infection. It may also for the same reasons not be used as an antibiotic of first choice for the treatment of infections for which gram-positive cocci are dominant pathogens despite its demonstration of higher ATSRF or ASF values. As indicated above, Tables of ATSFR and ASF values by these notations and as provided in the result presentations, must be taken only as a guiding document that is meant to provide valuable information for use by Hospital Therapeutic Committees, for example, in making decisions as to which antibiotics should be selected for first-line empiric treatments in given infections at their hospitals.

- Parenteral preparations are generally more expensive in terms of monetary costs than oral preparations. This is reflected in their having lower ASFs than oral preparations as seen in the case of cefotaxime injections in the results presentations (Table 4.2.19). Cost-wise, they may not be selected empirically rather than oral preparations except in situations where factors like the condition of the patient necessitates their use for initial treatment of infections or where their use in a specific infection is particularly indicated for other therapeutic reasons.
- A second empiric prescription of an antibiotic in the event of treatment failure when selection is based on antibiotics' ASF characteristics should be based on POAs. The antibiotic with the highest POA among the group of antibiotics should be prescribed in such circumstances regardless of its cost, provided it has not been the antibiotic used as first-line. In the event of either further treatment failure or the first-line antibiotic being the antibiotic with highest POA among the group of antibiotics from which the choice had been made then, culture sensitivity test results should form the basis of the antibiotic to be prescribed next in the management of the patient. This assumes, particularly in the case of inpatients, that culture sensitivity tests would have been requested before initiation of empirical antibiotic therapy.

- Consideration of which antibiotic selection method is preferred is proposed to depend on treatment policies of an institution with regard to whether or not antibiotic cost considerations should be a factor to be considered in the treatment of the infection. In situations where treatment cost recovery is borne by the institution, use of ASFs may assume importance in the selection of antibiotics. This would apply in Lesotho's public health institutions where inpatients and outpatients respectively pay fixed charges for their drug treatment regardless of the actual costs of the drugs used in patient management. In cases where patients bear the full cost of their prescriptions the antibiotic characteristics used in the selection of antibiotics of choice would depend more on patients' ability to pay for the costs of their treatment. Use of POA characteristics of the antibiotics may take precedence in such cases over ASFs. This may particularly be the case in situations of patients expressing willingness to pay for their antibiotic treatment regardless of how much they cost.

- **The extent of antibiotic coverage in the selection process**

Antibiotics that did not appear among antibiotics from which selections were made were antibiotics not tested against all pathogens implicated in the given infection. Such antibiotics by inspection of Tables 4.2.4 and 4.2.5 included mainly the aminoglycosides (gentamicin and amikacin)' nitrofurantoin and nalidixic acid which were tested only against GNB and not pathogenic gram-positive cocci isolates. Such antibiotics may be selected instead of suggested antibiotics for empirical prescription in treating indicated infections provided preliminary morphological identification of infecting organisms showed presence of GNB only and that their local activities towards these organisms can be considered greater than those of selected antibiotics. In the absence of any such information they may be prescribed only when results of culture sensitivity tests place them at an advantage in comparison with selected antibiotics for treating the infection.

The method developed for the rational selection of antibiotics in treating various infections empirically by this study is considered valid and reliable. Its clinical usefulness, however, depends greatly on the reliability of organisms' antibiotic sensitivity data used in determining defined characteristics required for the antibiotic selection processes. It is necessary for this reason for data for organisms' antibiotic sensitivity determinations to be collected prospectively and in a way as to address the above indicated limitations to

provide for a more authentic culture sensitivity set of data to be generated for use in determining more practically applicable POA or ATSRF and ASF values.

- **Limitations in the use of selected antibiotics in treating indicated infections according to results of study**

Selected antibiotics for use in treating infections as summarised in Table: 4.2.19 are intended to illustrate the applicability of the developed procedures in selecting antibiotics rationally or appropriately for effective empiric treatment of infections. As indicated in an earlier paragraph they may not be considered authentic selections of the antibiotics that could be empirically prescribed in the various clinical conditions. Limitations apparent in the nature of data used in determining antibiotic selection characteristics may be seen, as again mentioned in earlier paragraphs, as rather compromising the authenticity of selected antibiotics of choice in the empiric treatment of the various infections if compared to what could have been considered true results of the selection processes for clinical application if such limitations had been absent. It is important to note that limitations that may invalidate results of the selection process include the following as mentioned in discussions for results of Section 4.2.3.2:

- Policies of laboratories not to test all antibiotics against all major isolates. This did not allow for calculations of POAs of certain antibiotics to enable the selection process to cover as many as necessary antibiotics to provide a true picture of which antibiotic is truly therapeutically superior among all available antibiotics for selection in treating the infections.
- Very low frequencies of testing bacterial isolates against certain antibiotics. These were seen as not sufficiently validating statistically the calculated percentage sensitivities of the pathogens to the antibiotics to make their determined POAs as authentic as they should be. Ciprofloxacin, which by the results of the study has been identified as the preferred antibiotic for the empiric treatment of most infections, was most affected by this limitation (Table 4.2.4).
- The practice of prescribers sending specimens to laboratories for the identification of their microbial compositions and antibiotic sensitivity testing only after treatment failures as results of research Phase III indicated (Section 4.3.4). Implications of these are that frequency data actually used in determining organisms' percentage sensitivities to antibiotics, produced sensitivity data results for only a segment of specimens which could have been analysed for same determinations. In the view

of this study, differences in the percentage sensitivity patterns of organisms tested against antibiotics are likely to emerge if specimens are taken from all patients presenting with the various indicated infections to be analysed for their microbial compositions and antibiotic sensitivity. This view holding, there is a high possibility of different antibiotic selection characteristics as determined and used in the selection of antibiotics of preference in treating indicated infections, being obtained (Table 4.2.19) and hence the rendering of a different pattern of selected antibiotics of choice in the empiric treatment of indicated infections.

4.2.5 Summary: Research Phase II

This phase of the study investigated and reported results of pathogen associations with infections commonly diagnosed at study sites. It also reported local antibiotic sensitivity patterns of bacterial isolates to formulary antibiotics. Procedures developed for appropriate selection of antibiotics in the empiric treatment of infections based on mathematically quantified activity and cost characteristics of antibiotics had also been presented. Phase III of the study investigated possible factors contributing to observed patterns of antibiotic prescribing as established in research Phase I or compromised culture sensitivity test results data reported as a limitation in research Phase II. The evaluations and discussions of results of this phase of the study presented in the sections that follow.

4.3 EMPIRICAL RESEARCH PHASE III: FACTORS INFLUENCING ANTIBIOTIC PRESCRIBING PATTERNS IN LESOTHO

This phase of the study investigated factors that would influence prescribers' adherence to principles of antibiotic prescribing. It aims at ascertaining reasons that may explain observed patterns of antibiotic prescribing as established in Phase I of this study and also identifying problems considered as fomenting inappropriate antibiotic prescribing at study site hospital. Factors investigated generally included the extent of prescribers' use of microbiology laboratory facilities as aids to their diagnoses of infections and the influence of patient and prescriber- related factors on prescribers' decisions to prescribe antibiotics. Others included the extent of prescribers' adherence to principles of antibiotic prescribing within outpatient and inpatient settings, a test of prescribers' knowledge in principles of antibiotic prescribing as prerequisite factor for appropriate prescribing and antibiotic stock unavailability as a factor adversely affecting prescribers' choice of antibiotics.

4.3.1 Questionnaire response rate and demographic data (Questions 1-8)

The section focuses on the respondents' rate to questionnaires, their percentage distribution according to study sites and their demographic information on aspects of their qualifications, practice locations and types, availabilities of functional microbiology laboratories, their years of working experience, and their workloads.

4.3.1.1 Results

- **Response rate**

Table 4.3.1 shows numbers of questionnaires distributed to and collected from respondents within respective study site Health Service Areas (HSAs) and relevant questionnaire response rates. An analysis of the table indicates the following:

- Of a total of 67 questionnaires distributed 51 had been completed and returned, giving an overall response rate of 76.1%.
- Response rates to questionnaires at respective HSAs were 100% for Berea Health Service Area (HSA), 81.8% for Scott hospital HSA, 80% each for Maluti and Motebang hospital HSAs and 71% for Queen II hospital HSA.

- A majority of 43.0% of completed questionnaires came from the Queen II hospital HSA followed by 23.5% from Motebang HSA, 17.6% from Scott HSA, 9.8% from Berea HSA and 7.8% from Maluti HSA.

Table: 4.3.1 Frequencies of questionnaire distribution within and collection from study site Health Service Areas (HSAs)

HSA	Frequencies of questionnaire distribution and collection			Questionnaire Response rates from HSAs [$HSA_{(QRR)}$]
	Distributed	Completed and returned		
	$n_{(d)}$	$n_{(cr)}$	n%	
Berea	5	5	9.8	(100)
Maluti	5	4	7.8	(80.0)
Motebang	15	12	23.5	(80.0)
Queen II	31	22	43	(71.0)
Scott	11	9	17.6	(81.8)
Total	67	51	100	(76.1)

NB: Percentage distribution of completed and returned questionnaires (n%) without parenthesis = $(n_{(cr)}/\text{Total}_{\text{completed \&returned}})(100)$

Questionnaire response rate from HSAs [$HSA_{(QRR)}$] in parenthesis determined from $HSA_{(QRR)}$ = $(n_{(cr)}/ n_{(d)})(100)$

- **Percentage frequency distributions according to Respondents' demographic data**

Percentage frequency distributions of respondents according to their demographic data which included respondents' qualifications, practice types and practice locations, years of working experience, workload and patient types respondents seen are shown in Table 4.3.2, 4.3.3 and 4.3.4 and also Figure 4.3.1. Result indications in the Tables and Figure are as outlined below.

- **Qualification of respondents**
  - Respondents to questionnaires belonged to six qualification categories of doctors and nurses.
  - Doctors made up 76% of the total number of respondents and included 11 physician specialists, 3 surgical consultants, and 25 general practitioners who respectively represented 22%, 6%, and 48% of the total number of respondents.
  - Nurses totalled 17.6% of the total number of respondents. They included 8 nurse clinicians who constituted 16% of the total number of respondents and the other two were a registered nurses and nurse assistants who constituted 4% each of total number respondents.
  - Percentage frequency distribution figures of 92% for all respondents are composed of doctors and nurse clinicians, the two basic professional qualifications who by their educational training are entrusted with the professional responsibility of examining and treating patients.

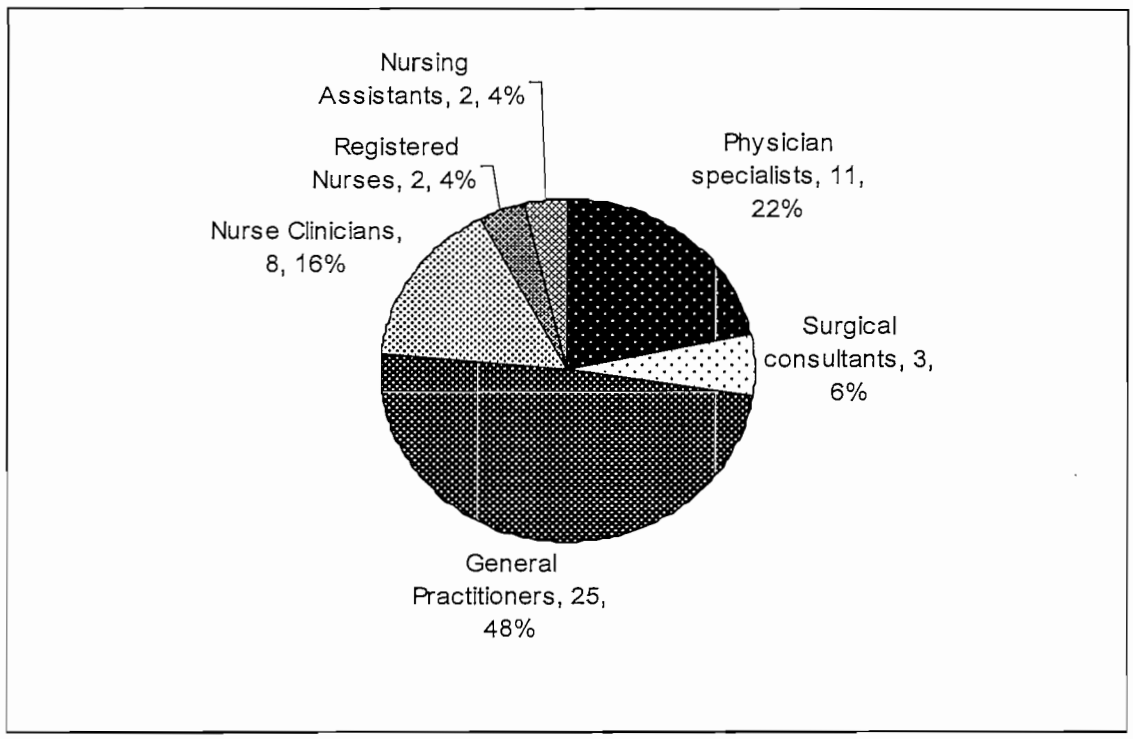

Figure 4.3.1 Percentage distribution of respondents according to qualification

- **Respondents' practice locations** (Table 4.3.2)
  - Respondents who practise in urban and rural areas respectively represent 80.4% and 19.6% of the total number of respondents.
  - All of the 11 physician specialists and 3 surgical consultant respondents practised in urban area hospitals. They respectively represented 26.8% and 7.3% of the total number of respondents who practiced in urban areas.
  - One out of 25 general practitioners practised in rural area situated health institutions and represented 10.0% of the total number of respondents who practised in rural areas. The rest i.e. 24 general practitioners practised in urban area hospitals. They represented 58.5% of the total number of respondents who practised in urban health institutions.
  - Of the total of eight respondents who are nurse clinicians, five practised in rural areas and three practised in urban health institutions. They represented 50.0% and 7.3% of the total number of respondents who respectively practised in rural and urban areas health institutions. All four registered nurses and nursing assistants practised in rural area health institutions. They represented 40.0% in total of the respondents practising in rural areas.
  - Of the total number of doctor and nurse clinician respondents who have been identified as the major prescribers of antibiotics within study sites HSAs 87.2% practised in urban areas as against 12.8% who practised in rural areas.

- **Respondents' practice types** (Table 4.3.2)
  - The majority of respondents worked in government health institutions (62.7%) in comparison with 23.5% and 13.7% who respectively worked in CHAL and either private and government or private and CHAL health institutions.
  - Of the 11 physician specialist respondents 54.5% and 9.1% respectively worked for government and CHAL institutions while 36.4% worked with either private and government or private and CHAL health institutions.
  - All three surgical consultant respondents practised in government health institutions.
  - Of the total number of general practitioner respondents, 64% worked in government health institutions, 24% worked in CHAL health institutions and 12%

worked with either private and government or private and CHAL health institutions.

- Of the total number of nurse clinician respondents, 62.5% and 37.5% worked respectively for government and CHAL health institutions.
- Both registered nurse and two nursing assistant respondents worked respectively in CHAL and government health institutions.

- **Respondents' years of working experience** (Table 4.3.2)
  - Of the total number of respondents, 60.8%, 23.5% and 15.7% respectively, had more than10 years, six to ten years and five or less years of experience working in their respective areas of qualifications.
  - The results revealed that 84.3% of respondents had six years and more than six years of working experience as against 15.7% who had one to five years of working experience including 9.1% of physician specialists, 20% of general practitioners, 12.5% of nurse clinicians and 50% of registered nurses.
  - With the exception of surgical consultants where 33.3% of respondents in the qualification category had more than 10 years of post- qualification experience, 50% or more of the respondents in all qualification categories had more than 10 years of working experience.

- **Respondents' workload** (Table 4.3.3)
  - The majority of respondents (60.8%) see and treat up to between 26 and 100 patients while as many as 17.6% see more than 100 patients a day.
  - Of the total number of 51 respondents 78.4% see and treat between 63 and more than 100 patients a day at their respective practice sites as against 21.6% who attend to 25 or fewer than 25 patients a day.
  - Of the total number of 39 doctors, 84.6% see and treat between 63 and more than 100 patients a day.
  - Of the total number of 8 nurse clinicians 75% similarly reported seeing and treating between 63 and more than 100 patients a day.
  - Of the total number of respondents 21.7% see and treat 25 or fewer patients a day.

- **Patient types seen and treated by respondents**
  - Of the total number of 51 respondents in all categories of qualifications, 35.3% attended to patients exclusively in outpatient departments.
  - Similarly and of total respondents in all categories of qualifications, 2.0% made up of one physician specialist attended to patients exclusively in inpatient departments.
  - Of the total number of 39 doctor respondents 82.1% treated patients in both outpatient and inpatient departments.
  - All 12 respondents in the nursing cadre reported treating only outpatients.

- **Availability and capacity of microbiology laboratories at respondents' practice sites**

Respondents' percentage frequency distribution according to their indications of availability to them of facilities for bacterial pathogen identification and culture sensitivity testing at their practice sites are as tabulated in Tables 4.3.5, 4.3.6 and 4.3.7 and outlined below.

- Of the total number of respondents, 70.6% (n = 36) reported having microbiology laboratories at their health facilities. Of this number 54.1% indicated that laboratories have the capacity to carry out morphological identification of bacterial pathogens and that available microbiology laboratories provide information on grams stain properties of microbial isolates routinely.
- Of the total number of respondents reporting availability of microbiology laboratory facilities at their practice sites, 43.2% indicated that available laboratories do not provide information on gram stain properties of microbial isolates.

Table 4.3.2 Percentage frequency distribution of respondents by their demographic data (Questions 1- 8)

Demographic data	Frequencies of respondents by qualifications and according to indications of demographic data													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	N%	n	n%	n	n%	N	n%	n	n%	n	n%	n	n%
Practice locations														
Urban	11	100 (26.8)	3	100 (7.3)	24	96.0 (58.5)	3	37.5 (7.3)	0	0.0 (0.0)	0	0.0 (0.0)	41	80.4 (100)
Rural	0	0.0 (0.0)	0	0.0 (0.0)	1	4.0 (10.0)	5	62.5 (50.0)	2	100 (20.0)	2	100 (20.0)	10	19.6 (100)
Total	**11**	**100 (21.6)**	**3**	**100 (5.9%**	**25**	**100 (49.0)**	**8**	**100 (15.7)**	**2**	**100 (3.9)**	**2**	**50 (3.9)**	**51**	**100 (100)**
Years of Experience:														
< or = 5 years	1	9.1 (12.5)	0	0.0 (0.0)	5	20.0 (62.5)	1	12.5 (12.5)	1	50 (12.5)	0.0 (0.0)	0.0 (0.0)	8	15.7 (100)
6 – 10 years	4	36.4 (30.8)	2	66.7 (15.4)	6	24.0 (46.2)	1	12.5 (7.7)	0	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	13	23.5 (100)
> 10 years	6	54.5 (20.0)	1	33.3 (3.3)	14	56.0 (46.7)	6	75.0 (20.0)	1	50 (3.3)	2	100 (6.6)	30	60.8 (100)
Total	**11**	**100**	**3**	**100**	**25**	**100**	**8**	**100**	**2**	**100**	**2**	**50**	**51**	**100**
Practice types														
Government Hospital	6	54.5 (18.2)	3	100 (9.1)	16	64.0 (48.5)	5	62.5 (15.2)	0	50.0 (3.0)	2	100 (6.1%	32	62.7 (100)
Christian Health Association of Lesotho Hospitals (CHAL)	1	9.1 (8.3)	0	0.0 (0.0)	6	24.0 (54.5)	3	37.5 (27.3)	2	50.0 (9.1)	0 (0.0)	0.0 (0.0)	12	23.5 (100)
Private and Government or Private and CHAL	4	36.4 (57.1)	0	0.0 (0.0)	3	12.0 (42.9)	0	0.0 (0.0)	0	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	7	13.7 (100)
Total	**11**	**100**	**3**	**100**	**25**	**100**	**8**	**100**	**2**	**100**	**2**	**50**	**51**	**100**

Notations: n% value determinations in bracket based on row totals
n% value determinations not in bracket based on column totals

Table 4.3.3 Frequency distribution of respondents by qualification and according to indications of daily patient workload (Questions 8)

Workload (Number of patients seen daily)	Frequencies of respondents by qualifications and according to indications of workloads													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	N%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
< or = 25	2	18.2	0	0.0	5	20.0	2	25.0	1	50.0	1	50.0	11	21.7
26 – 100	6	54.5	3	100	14	56.0	6	75.0	1	50.0	1	50.0	31	60.8
= or >100	3	27.3	0	0.0	6	24	0	0.0	0	0.0	0	0.0	9	17.6
Total	**11**	**100**	**3**	**100**	**25**	**100**	**8**	**100**	**2**	**100**	**2**	**100**	**51**	**100**

Table 4.3.4 Frequency distribution of respondents by qualification and according to patient types (Questions 7)

Patient types	Frequencies of respondents by qualifications and according to indications of patient types seen													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	n%	n	n%	n	n%	n	n%	n	n%	N	n%	n	n%
Outpatients	1	9.1	0	0.0	5	20	8	100	2	100	2	100	18	35.3
Inpatients	1	9.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	2.0
Both	9	81.8	3	100	20	80	0	0.0	0	0.0	0	0.0	32	62.7
Total	**11**	**100**	**3**	**100**	**25**	**100**	**8**	**100**	**2**	**100**	**2**	**100**	**51**	**100**

Table 4.3.5. Frequency distribution of respondents by qualification and according to availability of microbiology laboratory at practice sites.(Question 4)

Response indications	Frequencies of respondents by qualifications and according to indications of whether or not they have microbiology laboratories available at practice sites													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
Yes	11	100	3	100	22	88.0	0	0.0	0	0.0	0	0.0	36	70.6
No	0.0	0.0	0.0	0.0	3	12.0	8	100	2	100	2	100	15	29.4
No Response	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0	0.0	0	0.0	0	0.0
Total	**11**	**100**	**3**	**100**	**25**	**100**	**8**	**100**	**2**	**100**	**2**	**100**	**51**	**100**

Table 4.3.6. Frequency distribution of respondents by qualification and according to response indications of whether or not available microbiology laboratories have capacity to perform culture sensitivity tests. (Question 5)

Response indications	Frequencies of respondents by qualifications and according to indications of whether or not available microbiology laboratories have capacity to perform culture sensitivity tests													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
Yes	11	100	3	100	22	88.0	0	0.0	0	0.0	0	0.0	36	70.6
No	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
No Response	0	0.0	0	0.0	0.0	0.0	0.0	0.0	0	0.0	0	0.0	0	0.0
Not applicable	0	0.0	0	0.0	3	12.0	8	100	2	100	2	100	15	29.4
Total	**11**	**100**	**3**	**100**	**25**	**100**	**8**	**100**	**2**	**100**	**2**	**100**	**51**	**100**

Table 4.3.7 Frequency distribution of respondents with laboratory facilities by qualification and according to response indications of Whether or not available microbiology laboratories provide information on grams stain and morphological characteristics of pathogens (Question 6)

Response indications	Frequencies of respondents by qualifications and according to indications of whether or not available microbiology laboratories provide information on grams stain and morphological characteristics of pathogens													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
Yes	2	18.2	2	66.7	16	64.0	0	0.0	0	0.0	0	0.0	20	39.2 (54.1)
No	9	81.2	1	33.3	6	24.0	0	0.0	0	0.0	0	0.0	16	31.4 (43.2)
Sub total	**11**	**100**	**3**	**100**	**22**	**88.0**	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**	**36**	**70.6 (100)**
Not applicable	0	0.0	0	0.0	3	8.0	8	100	2	100	2	100	16	31.4
Total	**11**	**100**	**3**	**100**	**25**	**100**	**8**	**100**	**2**	**100**	**2**	**100**	**51**	**100**

4.3.1.2 Results Evaluation and Discussion

- **Questionnaire response rate**

As many of the health care professionals engaged in the diagnosis and treatment of infections as possible have been reached in this survey, though not all can be claimed to have been reached. The total number of 67 of questionnaires distributed, though small, is considered almost equivalent to the total number of prospective respondents expected to be included in the study as the sample size for the investigation aimed at and results from the analysis of data obtained are considered authentic, particularly in the face of observed high response rate to questionnaires. An overall response rate of 76.1% to questionnaires and between 71% and 100% such rates have been obtained for individual study site HSAs. Considering that mail questionnaire survey methods of data collection as noted by Neuman (2006:299), are seriously disadvantaged by difficulties of securing adequate response from targeted respondents, these reported response rates are considered high. This most probably is attributable to the method or strategy used in the questionnaire administration. As indicated in Section 3.5.3 the researcher interacted with respondents in the two processes of questionnaire distribution and collection. His explanation of the objectives of the study and availability to explain questions which respondents otherwise claimed they did not understand believably motivated respondents well enough to fill in and return the questionnaires.

- **Respondents' qualifications, practice locations and practice types**

- **Qualifications and practice locations**

Doctors in three qualifications of physician specialists, surgical consultants and general practitioners comprised the major group of respondents to questionnaires. Together with nurse clinicians who by their training are capable of diagnosing and treating common ailments with bacterial aetiologies, they constitute 92% of the total number of respondents (by calculations: Table 4.3.2). The two respondent categories by this percentage calculation may be considered as the principal prescribers of antibiotics at study sites. Of this principal group of prescribers of antibiotics so determined, 80.4% (Table 4.3.2) practise in urban area hospitals or clinics from which data on antibiotic prescriptions assessed for their appropriateness as entailed in Phase I of this study, were collected. Opinions of these qualifications of respondents on factors influencing patterns of antibiotic prescribing as current phase of the study investigates, are

considered for this reason to be of importance in explaining or confirming observed patterns of antibiotic prescribing established by results of the indicated phase (Phase I) of the research. Registered nurses and nursing assistants, with an 8% representation of total respondents constitute a minute percentage of health care professionals involved in infection diagnosis and antibiotic prescribing within study site HSAs (Table 4.3.2). Together with the majority of nurse clinicians, they are viewed to practise at health centres located in rural areas. Unlike health institutions sited in urban areas, data on antibiotic prescriptions analysed for their appropriateness were not collected from these rural area health centres and opinions of these categories of respondents on antibiotic prescribing were not considered relevant to explanations offered for patterns of antibiotic prescribing as Phase I of the study established.

The observed pattern of distribution of the different qualifications of respondents between urban and rural area health establishments suggests that nurses generally are used more often by health authorities to extend health services to rural areas of the country as compared to doctors who mainly are retained in hospitals and clinics situated in urban areas. The curriculum for training registered nurses has a course in microbiology and parasitology that has as part of its outline course contents that relates to specific microorganisms to infections they cause. It, however, excludes formal lessons and training in the practical diagnosis and treatment of infections (National Health Training College (NHTC), 2004:64; National University of Lesotho (NUL), 2003:41). With this level of lessons received in microbiology in their training programmes registered nurses can be said not to have received practical training in infection diagnosis and treatment to qualify them as prescribers of antibiotics. Nursing assistants are trained in aspects of nursing that qualifies them to assist registered nurses (Government Gazette, 1998:49(1):106 &107) and are supposedly also not trained in the practical aspects of infection diagnosis and treatment. It is considered inappropriate for the two qualifications in the nursing cadre to be involved in antibiotic prescribing. Having said this, though, it is acknowledged that lack of manpower within the health sector as evidenced by the low doctor-to-patient ratio of 1:20,000 in Lesotho (United Nations, 2003: 33), may leave health policy makers in the country with the one option of extending health services to remote areas, including disease diagnosis and treatment, through the services of nurses. This is confirmed to be the case by findings of this study. The involvement of registered nurses and nursing assistants in the diagnosis and treatment of infections is

envisaged to promote inappropriate antibiotic prescribing with its resultant deleterious effects. If these qualifications of the nursing cadre are going to be deployed at these levels of health delivery, then they need to be given the requisite training that would expertly equip them to face up to the responsibilities of providing clinical services in the area of antibiotic use.

- **Respondents' practice types**

Most of the physician specialists and all surgical consultants work in government health institutions as compared to a lower percentage of nurse clinicians working in CHAL institutions (Table 4.3.2). This pattern of percentage distribution of respondents between the two types of health institutions defining respondents' practice types could be partly explained by the larger sizes of government owned study site hospitals, compared with the smaller sizes of CHAL owned hospitals selected for the study. It is also reflective of the situation where more senior doctors seemed to be engaged for services in government than CHAL owned health institutions.

Respondents who indicated practising in both private and government or private and CHAL health institutions work with institutions owned by non-governmental organisations (NGOs) while at the same time attending to patients in government and CHAL health institutions. The category of respondents included principally doctors working with Baylor hospital for children with HIV and AIDS who at the same time render services in the children's ward at the Queen II hospital. It also included doctors working with Medicine Sans Frontiers (MSF) who also see and treat patients at the outpatient department of Scott hospital. By the nature of services they render these doctors were considered as practising in public health institutions like all other respondents and as such, their opinions on factors influencing antibiotic prescribing as investigated were taken as reflecting opinions of doctors working solely in public health institutions.

The practice trend of utilising nurses without formal training in disease diagnosis and treatment in extending clinical services to rural areas of study site HSAs, applies equally to both government and CHAL health institutions as results of the study depict. The call to provide this cadre of qualifications the training they need in infection diagnosis and antibiotic prescribing by this finding is directed equally to health policy makers in both CHAL and government health institutions.

- **Respondents' years of working experience**

Working experience connotes knowledge a practitioner acquires by virtue of what he learns informally while in practice. (Eraut, 2004;247) defines informal learning as learning that takes place in the spaces surrounding activities and events with a more overt formal purpose that involve a combination of learning from other people and learning from personal experience. The author recognised knowledge acquisition and use in complex situations as achievable through learning about other people and learning to use scientific and other forms of academic knowledge in practice contexts (Eraut, 2004;248). In a chapter they wrote on experience-based learning in the book "Understanding adult education", published 14 years ago, Andresen *et al.* (1995:225) defined learning as a process whereby knowledge is created through transformation of experience. Learning by experience as the above literature references tend to imply is seen as a process that essentially develops from the learner's continuing contact with his or her environment and the transformation of experiences he or she gained from such contact into knowledge. Although not considered always true in practice, one would normally expect that the more years of practice respondents have the more experience they gain in diagnosing and treating infections and hence the more capable and efficient they will be in their manner of prescribing antibiotics.

By logic, theories in bacteriology and general principles of antibiotic prescribing that respondents supposedly apply as they prescribe antibiotics would much depend on what they can recall or remember from lessons on these topics that they were taught, presumably, during their respective training programmes. Considering that persons forget what they learn with time and that there is a strong possibility of respondents' forgetting theoretical aspects of antibiotic prescribing as time passes one could raise the question of whether or not antibiotic prescribing capabilities of prescribers indeed improve the longer they stay in practice. This question becomes relevant, particularly in absence of continuing education programmes in professional practice environments to keep practitioners abreast with theories and new developments in their professional areas of practice. By common knowledge, regular presentation of such education programmes for health care professionals in the area of rational prescribing of drugs, antibiotics inclusive, is a missing link in doctors' and nurse clinicians' professional practice within the health delivery system of Lesotho. This indicates that prescribers' ability to prescribe antibiotics appropriately would be determined more by knowledge

they already have in the subject area of antibiotic prescribing than knowledge they are likely to acquire through continuing education programmes while in practice. The possible decline of such knowledge with time as postulated above may have the potential of negating the beneficial effects of long years of prescribers' working experience. The majority of respondents have more than 10 years of working experience, as results of this study showed. In the aspect of this survey which tested prescribers' knowledge in principles of antibiotic prescribing (Section 4.3.5; Table 4.3.26) 84.3% of respondents demonstrated a performance level range that fell in the assessment category depicting respondents as having very poor to fair knowledge in principles of antibiotic prescribing. This level of performance by the indicated percentage majority of respondents is considered poor enough to give credence to thoughts that long years of stay in practice may not necessarily improve prescribers' ways of prescribing antibiotics particularly in absence of continuing education programmes.

Studying predictors of inappropriate prescribing of antibiotics among primary care physicians, Cadieux *et al.* (2007:881) established that rates of inappropriate antibiotic prescribing among the indicated study subjects actually increased with increased numbers of years in practice. Giving reasons for this the researchers indicated that physicians tend to "soften" to patients' demands for antibiotics with increased time in practice. In spite of their postulation of different reasons in explanation of this established pattern of antibiotic prescribing among physicians, the findings of Cadieux *et al.* (2007:881) confirmed findings of this research with respect to the impact of prescribers' years of practice and their ability to prescribe antibiotic appropriately.

- **Respondents' workload**

The majority of doctors (84.6%) and 75% of nurse clinician respondents reported seeing between 26 and 100 and up to more than 100 patients a day. Doctor respondents seeing both inpatients and outpatients and constituting up to 82% (32 out of 39) of all doctors or together with 75% (6 out of 8) of nurse clinicians, representing 80.9% (38 out of 47) of doctor and nurse clinician respondents seeing outpatients reportedly have such workload (Table 4.3.3). Interpreted in terms of time spent per patient, this means a prescriber consulting and treating patients for a maximum of 8 working hours a day as is the case in Lesotho, and seeing 63 and up to more than 100 patients a day spends approximately 8 minutes or 5 or less minutes to diagnose and treat each patient's presenting clinical condition.

Raymont *et al.* (2005: 4&6) in a national primary medical care survey in which they investigated New Zealands general practitioners' characteristics and workloads in year 2001, recorded that general practitioners (GPs) in New Zealand on average have a workload of about 26.4 patients per day. They described this as lying within international range of doctor's' workload. Compared to this workload, only 21.6 % of respondents were seen to have a workload lying with international range. The rest (88.4%) with the above indicated composition of doctors and nurse clinician respondents seeing between 26 and 100 and more than 100 patients a day can be considered as having workloads far above the internationally acceptable workload range for GPs.

The effect of a high workload on the performance of doctors has been studied by a number of researchers, some of which are as referenced below. Howard and Gaba (2004:975) determined intern doctors' workload in terms of long working hours (60 to 80 hours a week) in busy hospital environments. They concluded from their findings that a high workloads impair the performance, worsened the mood of this category of doctors and compromised patient safety. In a similar study, Landrigan *et al.* (2004:1842) also found a high workload of interns determined in terms of longer hours of work to be associated with increased rates of medical errors the trainee doctors make. With regard to the effect of workload on practising doctors' capability to prescribe antibiotics appropriately, Cadieux *et al.,* 2007:881) determined that primary health care physicians with high volume practices were more likely than similar physicians with low volume practices to prescribe antibiotics inappropriately. The researchers Cadieux *et al.* (2007:881) indicated that similar associations were observed among Spanish and Italian doctors. Practice volume according to them, is a complex measure that may reflect interaction with patients and a lack of time for patient consultation.

These research findings have established the deleterious effects of a high workload on prescribers' performance and their abilities to prescribe antibiotics appropriately. The eight (8) or five (5) or fewer minutes seen to be spent by majority of doctors in consulting and treating a patient by this study is considered far too low for efficient patient management. By interpretation, and as Cadieux *et al.* (2007:881) indicated, this means less time being spent by a majority of respondents on patient consultation. This has the potential of resulting in less efficient diagnosis and treatment of infections with higher chances of antibiotics being inappropriately prescribed. High prescriber workload by

findings of this study has been established as an attendant relative feature of health delivery in the primary and tertiary health institutions of study sites. It may be recognised as a factor that is prospectively seen as compromising efficient diagnosis and treatment of infections and hence appropriate prescribing of antibiotics.

- **Types of patients respondents see and associations of patterns of antibiotic prescribing with respondent qualifications**

In the exception of five (5) general practitioner respondents who see and treat patients exclusively in outpatient departments all doctor respondents see and treat inpatients. Similarly, and except for one (1) physician specialist who sees and treats patients exclusively in inpatient departments, all doctor respondents see and treat outpatients. All doctor respondents were also seen to practise exclusively in urban health institutions where prescriptions were collected and assessed in study Phase I. All respondents in the category of nurses on the other hand practise in outpatient settings, with three (3) out of this number reportedly practising in urban health institutions where prescriptions were collected and analysed for their appropriateness. Of all respondents who saw and treated patients in outpatient settings in urban health institutions of study sites 92.1% by results analysis, were seen to be doctors as against 11.9% who were nurses (Table 4.3.4). from these considerations it can be inferred that all inpatient and a large majority of outpatient prescriptions analysed for their appropriateness in research Phase I were written by doctors. Patterns of antibiotic prescribing, as reportedly established by results of research Phase I (Tables 4.1. and 4.1.21), are hence attributable principally to manners in which doctors, rather than nurses, prescribed antibiotic at study sites.

From these discussions and also from results of research Phase I and percentage distributions of prescribers according to years of experience and workloads it can be inferred that

- doctors' years of practice experience do not significantly exercise on impact on their manner of antibiotic prescribing for both inpatients and outpatients ; and
- doctors' workloads appear to be a significant factor that may hamper appropriate prescribing of antibiotics, particularly for inpatients.

- **Availability of microbiology laboratory facilities**

All the doctor respondents (n=39) with the exception of two reported availability of laboratory facilities at their practice sites (Table 4.3.5). All nurse respondents reported not having laboratory facilities at their practice sites. The majority (54.1%) of respondents reporting availability of laboratory facilities at their practice sites, indicated that available laboratories are capable of carrying out morphological identification of bacterial pathogens and that they do provide information on grams stain properties of microbial isolates routinely either separately or along with culture sensitivity test (CST) results (Table 4.3.7).

Evaluations of respondents' indications of patient types they see and the association of patterns of antibiotic prescribing with respondent qualifications indicate that both inpatient and outpatient prescriptions assessed in study Phase I were principally written by doctor respondents. Results of Phase I showed that of all inpatient prescriptions assessed for their appropriateness only 1.3% (4 out of 307) were seen to be written based on results of culture sensitivity tests (Table 4.1.1). Of all outpatient prescriptions assessed for their appropriateness, none was seen to be prescribed based on results of culture sensitivity tests (CST) (Figure 4.1.8). Interpreted from perspectives of these Phase I results, the majority (94.9%) (37 out of 39) of all doctor respondents reporting availability of medical microbiology laboratories at their practice sites can be construed to mean doctors' rare use of microbiology laboratory facilities at their disposal to aid their diagnosis and appropriate prescribing of antibiotics to treat infections.

The non-provision of information on grams stain and other morphological properties of microbial isolates in the opinions of 43.4% of respondents reporting availability of microbiology laboratory facilities at their practice sites, indicates operational inefficiencies in the use of laboratory facilities. As a factor the availability and functional capabilities of microbiology laboratories at respondents' practice sites *per se* is not seen as limiting respondents' ability to prescribe antibiotics appropriately. The inefficient use of laboratory facilities as on the other hand is postulated as a factor limiting prescribers' ability to prescribe antibiotics appropriately based on laboratory provided information. Though not investigated, deficiencies in operational mechanisms that coordinate prescribers' request for laboratory tests and the provision of feedbacks to such requests from laboratories are identified as most likely reasons for prescribers' inefficient use of

microbiology laboratory facilities and hence their non-use of laboratory-based information in making decisions in the diagnosis and treatment of infections.

4.3.2 Determining the extent to which patient and prescriber related factors influence prescribers' decisions to prescribe antibiotics (Question 9)

A number of factors relating to the characteristics of both patients and prescribers may influence prescribers' decisions to prescribe antibiotics for the wrong reasons and hence serve as contributing factors to inappropriate prescribing and use of antibiotics within given population groups. Some such factors as investigated in this study are patient related and included prescriber influence by requests of patients for or their expectations to be treated with antibiotics.

Other factors investigated are prescriber related and included desires of prescribers to prescribe antibiotics according to their self convicted reasons for antibiotic use including, for example, prescribers' desire to eliminate infections when there is no proof of their existence or preventing anticipated infections when there are no reasons to suspect such infections will occur. The extents to which these factors assume importance in determining whether respondents prescribe antibiotics or not and hence their roles as contributing factors to inappropriate prescribing of antibiotics have been determined and presented in this section.

4.3.2.1 Results

Percentage distributions of respondents according to degrees to which investigated factors influence their decisions to prescribe antibiotics are shown in Tables 4.3.8 through 4.3.13 and summarised in outline as presented below.

- **Prescribing antibiotics in consideration of biomedical factors or patients' clinical condition (Question 9i) (Table 4.3.8)**
  - Of the total number of respondents involved in the survey, 72.5% reported considering biomedical factors or factors relating to the patients' clinical condition to a major degree when they prescribe antibiotics for patients.
  - A further 15.7% indicated that they considered such factors to a minor degree while 7.8% said they did not consider it at all when they prescribed antibiotics.

Table 4.3.8 Frequency distributions of respondents according to degrees to which patient biomedical factors affect their decisions to prescribe antibiotics (Question 9(i))

Degree indications of effects of factor	Frequencies of respondents by qualifications and according to degrees to which patient or biomedical factors affect their decisions to prescribe antibiotics.													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
Not all	1	9.1	0	0.0	3	12.0	0	0.0	0	0.0	0	0.0	4	7.8
Minor degree	1	9.1	0	0.0	4	16.0	2	25.0	0	0.0	2	100	8	15.7
Major degree	9	81.8	2	66.7	17	68.0	6	75	2	100	0	0.0	37	72.5
No response	0	0	1	33.3	1	4.0	0	0.0	0	0.0	0	0.0	2	3.9
Total	**11**	**100**	**3.0**	**100**	**25**	**100**	**8**	**100**	**2**	**100**	**2**	**100**	**51**	**100**

Table 4.3.9 Frequency distributions of respondents by qualifications and according to degrees to degrees to which they are made to prescribe antibiotics to satisfy patients' request for them (Question 9(ii))

Degree indications of effects of factor	Frequencies of respondents by qualifications and according to degrees to which they prescribe antibiotics to satisfy patients' request for them													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	n%	n	n%	n	n%	n	n%	n	N%	n	n%	n	n%
Not all	11	100	2	66.7	21	84.0	1	13.0	1	50.0	2	100	38	74.5
Minor degree	0	0.0	0	0.0	3	12.0	3	37.0	0	0.0	0	0.0	6	11.6
Major degree	0	0.0	1	33.3	1	4.0	4	50.0	1	50.0	0	0.0	7	13.7
No response	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Total	**11**	**100**	**3.0**	**100**	**25**	**100**	**8**	**100**	**2**	**100**	**2**	**100**	**51**	**100**

- The majority of respondents reported they would consider patients' clinical conditions to a major degree as they prescribed antibiotics and included 81.8% (9 out of 11) of physician specialists, 100% (3 out of 3) of surgical consultants, 68% (17 out 25) general practitioners, 75% (6 out of 8) nurse clinicians and both (2) registered nurses.

- **Prescribing antibiotics to satisfy patients' request (Question 9ii) (Table 4.3.9)**

  - A majority (74.5%) of the respondents indicated not being influenced at all by their desire to satisfy patients' request for antibiotics while 11.6% (n = 6) and 13.7% (n = 7) respectively indicated they were influenced to minor and major degree.

- **Prescribing antibiotics to satisfy patients' expectations regarding treatment they hoped to get for their ailment (Question 9iii) (Table 4.3.10)**

To the question of whether respondents were influenced by their desire to satisfy patients' expectations regarding type of treatment they expected to receive as they prescribed antibiotics,

- 84.3% indicated they were not at all influenced by this factor;
- 3.9% said they were influenced to a minor degree; and
- 9.8% indicated they were influenced to a major degree.

- **Prescribing antibiotics for desire to eliminate infections in cases of unclear diagnosis (Question 9 iv) (Table 4.3.11)**

In response to the question of whether or not they prescribed antibiotics for their desire to eliminate infections in cases of unclear diagnosis,

- 41.2% indicated that their decisions to prescribe antibiotics were influenced to a major degree by their desire to eliminate infections in cases of unclear diagnosis;
- 49.0% said they were influenced to a minor degree only by the factor; and
- 3.9% indicated they were never influenced at all by this factor as they prescribed antibiotics.

Table 4.3.10 Frequency distributions of respondents by qualifications and according to degrees to which they are made to prescribe to satisfy patients' expectations regarding treatment they hoped to get for their ailment (Question 9(iii))

Degree indications of effects of factor	Frequencies of respondents by qualifications and according to degrees to which they are made to prescribe to satisfy patients' expectations													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
Not all	11	100	2	66.7	24	96	3	37.5	1	50	2	100	43	84.3
Minor degree	0	0.0	0	0.0	0	0.0	2	25.0	0	0.0	0	0.0	2	3.9
Major degree	0	0.0	1	33.3	0	0.0	3	37.5	1	50	0	0.0	5	9.8
No response	0	0.0	0	0.0	1	4.0	0	0.0	0	0.0	0	0.0	1	2
Total	**11**	**100**	**3.0**	**100**	**25**	**100**	**8**	**100**	**2**	**100**	**2**	**100**	**51**	**100**

Table 4.3.11 Frequency distributions of respondents by qualifications and according to degrees to which they are made to prescribe antibiotics by their desire to eliminate an infection in cases of unclear diagnosis (Question 9iv)

Degree indications of effects of factor	Frequencies of respondents by qualifications and according to degrees to which they are made to prescribe antibiotics by their desire to eliminate an infection in cases of unclear diagnosis													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
Not all	1	9.1	0	0.0	1	4.0	0	0.0	0	0.0	0	0.0	2	3.9
Minor degree	4	36.4	2	66.7	11	44.0	5	62.5	0	0.0	0	0.0	25	49.0
Major degree	6	54.5	0	0.0	12	48.0	2	25.0	2	100	2	100	21	41.2
No response	0	0.0	1	33.3	1	4.0	1	12.5	0	0.0	0	0.0	3	58.8
Total	**11**	**100**	**3.0**	**100**	**25**	**100**	**8**	**100**	**2**	**100**	**2**	**100**	**51**	**100**

Table 4.3.12 Frequency distribution of respondents by qualifications and according to degrees to which their decision to prescribe antibiotics is influenced by their desire to prevent an infection even if bacterial infection is ruled out (Question 9v)

Degree indications of effects of factor	Frequencies of respondents by qualifications and according to degrees to which their decision to prescribe antibiotics is influenced by their desire to prevent an infection													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
Not all	2	18.2	0	0.0	3	12.0	1	12.5	1	50	0	0.0	7	13.7
Minor degree	3	27.3	1	33.3	7	28.0	2	25.0	1	50	1	50.0	15	29.4
Major degree	6	54.5	1	33.3	12	48.0	5	62.5	0	0.0	0	0.0	24	47.1
No response	0	0.0	1	33.3	3	12.0	0	0.0	0	0.0	1	50	5	9.8
Total	**11**	**100**	**3.0**	**100**	**25**	**100**	**8**	**100**	**2**	**100**	**2**	**100**	**51**	**100**

Table 4.3.13 Frequency distributions of respondents by qualifications and according to degrees to which their past Experiences influence their decisions to prescribe antibiotics (Question 9vi).

Degree indications of effects of factor	Frequencies of respondents by qualifications and according to degrees to which their past experiences influence their decisions to prescribe antibiotic													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
Not all	1	9.1	0	0.0	3	12.0	1	12.5	1	50	0	0.0	6	11.8
Minor degree	3	27.3	0	0.0	7	28.0	4	50.o	0	0.0	1	50.0	15	29.4
Major degree	6	54.5	2	66.7	15	60	3	37.5	1	50	0	0.0	27	52.9
No response	1	9.1	1	33.3	0	0.0	0	0.0	0	0.0	1	50.0	3	5.9
Total	**11**	**100**	**3.0**	**100**	**25**	**100**	**8**	**100**	**2**	**100**	**2**	**100**	**51**	**100**

- **Prescribing antibiotics for wanting to prevent an infection even if bacterial infection is ruled out (Question 9v) (Table 4.3.12)**

  - A significant 47.1% (n=24) of respondents, almost half of the total number of respondents, indicated they were influenced to a major extent by their desire to prescribe antibiotics for purposes of preventing an infection even if they had ruled out bacterial infections as aetiological agents.

- **Deciding to prescribe antibiotics on the basis of past experiences with similar infections (Question 9vi) (Table 4.3.13)**

  - Of those who claimed not being influenced at all by their past experiences when they decided to prescribe antibiotics for their patients were 9.1% (1 out of 11) of physician specialists, and 12% (3 out of 25) of general practitioners and 12.5% (1 out of 8) of nurse clinicians, 50% (1out of 2) of registered nurses. They represented in total 11.8% (n= 6) of respondents.

4.3.2.2 Results Evaluation and Discussion

Antibiotics are prescribed specifically to treat infections or to prevent infections (Chambers, 2005:1164) in unique cases where possible infections are envisaged as for example in surgical operations or in cases where implanted prosthetic devices in a tissue, catheters or concurrent clinical conditions in the patient increase risks of infection (Bratzler & Houck, 2005:400; Gugliemo, 2008: 56-7). To be effective when used for any of these purposes, antibiotics need to be prescribed judiciously and appropriately. The term "judicious" when used with reference to antibiotic prescribing is defined according to Gaur and English (2006:343), as entailing the prescribing of this class of drugs only when they are indicated, cost- effectively selected to provide antimicrobial coverage for the diagnosed infection and prescribed at an optimal dose for a duration of action that ensures complete elimination of infecting pathogens. By the definition of WHO Global Strategy for Containment of Antimicrobial Resistance, appropriate use of antibiotics means the cost-effective use of these drugs in ways that maximise their clinical therapeutic effect while minimising both drug -related toxicity and the development of antimicrobial resistance (World Health Organization, 2001:15). By inference from the above definitions, inappropriate or injudicious use of antibiotics undoubtedly has the

potential of resulting in treatment failures of infections while giving rise to the development of microbial resistance to antibiotics.

Gaur and English (2006:343), as they further indicated in their paper noted that in developing countries over the counter access to antibiotics is recognised as an important contributor towards injudicious or inappropriate use of antibiotics while in developed countries prescriber practice and patient characteristics assume more importance as factors contributing to the problem. The authors cited results of many studies in the developed countries and attempted to provide an understanding to the causes of injudicious use of antibiotics. Essentially they indicated the following as some characteristics of health service providers that could lead to inappropriate prescribing of antibiotics (Gaur & English, 2006:343). These include:

- the practice of prescribing antibiotics for diagnosis suggestive of viral infections in outpatient settings for example being very common among staff physicians;
- lack of knowledge among prescribers being a contributor to inappropriate antibiotics use,;
- the dispensing of antibiotics by other health service providers other than physicians with variable training backgrounds including even those with no medical training; and
- dispensing doctors making profit from both prescribing and dispensing antibiotics having the tendency to prescribe antibiotics more for financial gains than for their appropriateness of conditions they prescribe them for.

Referring to patient characteristics seen as influencing doctors' decision to prescribe antibiotics for their patients, the authors indicated particularly that in instances where a parent or child received an antibiotic prescription for an illness in the past, that past experience engenders expectations that the same therapy would be required in the event of such symptoms recurring. Patients' expectations and views and doctors' concern that patients may otherwise re-consult, according to them and as results of some studies indicated, were seen to have a powerful effect on doctors' decisions to prescribe antibiotics (Gaur & English, 2006:346). According to the authors, doctors indeed experience real pressures from their patients to prescribe antibiotics for conditions for which the drugs may not be needed.

No studies showing the extent to which prescriber and patient characteristics contribute to inappropriate prescribing of antibiotics have been done in Lesotho. Results of investigations into the existence of some of these factors as reported above and the impact they may be have on appropriateness of antibiotic prescribing are as discussed below.

- **Considerations of patient- related biomedical factors in antibiotic prescribing**

A judicious prescription of an antibiotic entails as a first principle, establishing that such an antibiotic is indicated for the condition treated before it is prescribed. This by interpretation means antibiotics must be prescribed in response to results of need assessment tests in which the prevailing clinical condition of the patient would have been properly diagnosed and the need for antibiotics established before decisions are taken to prescribe them. The situation requires a maximum expectation of 100% respondents indicating that they consider biomedical factors or patients' clinical condition before deciding to prescribe antibiotics. The reported 7.8% of respondents indicating that they do not consider this factor at all or the 15.7% who indicated considering the factor only to minor degrees as they decide to prescribe antibiotics, have significantly established prescribers' non-consideration of biomedical factors relating to the patient in all cases of antibiotic prescribing. This contravenes principles of appropriate antibiotic prescribing and is considered a factor that may adversely contributes to inappropriate prescribing of antibiotics. Its importance in this regard is underscored with the majority of respondents admitting not considering the factor when they decide to prescribe antibiotics being doctors (physician specialists and general practitioners) and nurse clinicians, the identified major prescribers of antibiotics in the country.

By results of study Phase 1, as high as 17.6% and 12.1% of antibiotic prescriptions were seen to be prescribed respectively for clinical conditions for which antibiotic prescriptions were not justified in both inpatient and outpatient departments (Table 4.1.1 & Figure 4.1.8). These determined percentages of the classification group of prescriptions (Category F) are comparable to a total 23.5% of respondents (Table 4.3.7) who are disposed to prescribing antibiotics for unjustified reasons because of their manner of antibiotic prescribing as determined by their indications of not being influenced at all or influenced to a minor extent only by biomedical factors relating to the patient. In some ways this can be assumed as establishing an association between prescribers' non-

consideration of biomedical factors relating to patients as they decide to prescribe antibiotics and their tendencies to prescribe this class of drugs for clinical conditions for which their uses are not justified. It postulates the existence among prescribers of the culture of antibiotic prescribing for patients' complaints irrespective of whether or not such complaints have bacterial aetiologies and underscores the negative contribution of such culture among the study population of prescribers to inappropriate prescribing of antibiotics.

- **The impact of factors of prescribers' desire to prescribe antibiotics to satisfy patients or prevent infections**

Prescriber- related factors that may determine their tendencies to prescribe antibiotics for purposes for which the drugs are not needed were investigated by three questions that sought to establish whether prescribers prescribe antibiotics

- to satisfy whims and conceptions of patients on their needs of antibiotics;
- for infections where they do not exist; or
- to prevent infections when there are no justifiable reasons to associate currently treated clinical conditions with anticipated infections.

Results of investigations into the effect of these factors as tabulated and outlined above indicate that significant percentages of prescribers of all qualifications are influenced by these factors and would indeed at one time or the other prescribe antibiotics for these reasons. For reasons that these manners of antibiotic prescribing may have a negative impact on appropriateness of antibiotic prescriptions they are considered as major factors fundamentally contributing to inappropriate prescribing of antibiotics by the population of prescribers studied.

- **Prescribing antibiotics to satisfy either patients' requests for them or their expectations of treatments they hoped to receive**

As many as 25.5% of respondents in all qualification categories of prescribers, would, at any one time or the other, prescribe antibiotics for reasons of patients requesting for them. Nurse clinicians, with a majority of 87.5% of them collectively indicating that they are questing for them, are particularly disposed to prescribing antibiotics to satisfy patients influenced to prescribe antibiotics to minor and major degrees on the basis of patients re' requests.

Of a total number of respondents 13.7% (Table 4.3.9) were observed to be influenced to minor and major degree by their desires to satisfy patients' expectations and would hence sometimes prescribe antibiotics for the reasons of patients expecting to be given such treatment for their ailments. Nurse clinicians here again are most likely to prescribe antibiotics for this reason

The 25.5% and 13.7% of respondents disposed to prescribing antibiotics to either satisfy requests patients make or satisfy their expectations of treatment they hoped to be given for their ailments are indicative of chances of antibiotics being prescribed inappropriately for the respective reasons by respondents. By this interpretation the factors of prescriber influences by patients' demand for antibiotics or patients' expectations to be treated with antibiotics are observed to exist and possibly are significant contributors to injudicious prescribing of antibiotics among the study population of prescribers.

The disposition of nurse clinicians to prescribe antibiotics most often for these patient-oriented factors, in comparison with other prescriber qualifications, is difficult to explain. The prescriber qualification may only be considered by these results as being most dependent on what patients suggest to them as their treatment preferences as basis for their decisions to prescribe antibiotics. This may be attributable to a lack of knowledge and confidence nurse clinicians need in the diagnosis and treatment of infections to enable them to make independent knowledge- based decisions on whether or not a patient should be treated with antibiotics. It could also be an experience driven factor emanating from previous treatment successes most nurse clinician respondents might have had in their practices. Gaur and English (2006:345) attributed lack of knowledge to inappropriate antimicrobial prescribing from conclusions they drew from results of a study by Hui *et al.* (1997) in which the appropriateness of antibiotic treatments provided by various health workers in China was assessed. Mangione-Smith *et al.* (1999:716) studying the effects of parent expectations on paediatrician antibiotic prescribing noted that on occasions physicians thought a parent wanted antimicrobial prescriptions, otitis media and sinusitis were both significantly more likely to be diagnosed. This result associates parental suggestions for antibiotics to actually diagnosed bacterial infections and indicates situations as observed in the cases of nurse clinician respondents, when prescribers' decision to prescribe antibiotics may become influenced by patients' treatment expectations or their requests for antibiotics through past experiences.

Registered nurses and nurse assistants responding to questionnaires form a minority of 8% of the total of respondents (Table 4.3.2) and their group pattern of prescribing antibiotics is not envisaged to have any significant effect on what would be identified as a general trend of antibiotic prescribing among the study population of prescribers. The observation that almost all respondents of the two qualifications in the nursing cadre indicated that they did not prescribe antibiotics to satisfy patients' requests or meet their expectations of treatment, may be explained from the literacy level of patient populations they see and treat. A display of good knowledge of infection diagnosis and treatment, which one would assume enabled them to take independent decisions on whether patients they treat need antibiotics or not is rather less likely. The two qualification categories of respondents work in the rural areas where literacy levels of patients are low. The scope of this study did not include an investigation on the literacy standards of patients respondents see and treat. Indications, however, are those respondents working in health service institutions in remote rural areas where registered nurse and nursing assistant respondents were posted may not come into contact with the elite and more literate population of patients. A literate population of patients would supposedly know enough about drugs that they are treated with to be able to make specific requests of what they think they should be given for their ailments. Patient oriented pressures on prescribers regarding drugs they would want to be prescribed in treatment of their ailments may be assumed to be absent at this level of health care leaving respondents more often than not to prescribe their choices of drugs rather than what patients would request to be prescribed for them. Further research is needed to substantiate or disprove this speculation.

- **The impact of factors of prescribers' quests to eliminate or prevent infections on appropriateness of antibiotic prescriptions**

A significant majority (90.2%) of respondents in total more influenced to major and minor degrees by their quests to prescribe antibiotics for purposes of eliminating underlying bacterial infections in the event of not being sure of their diagnosis (Table 4.3.11). On a similar note, a majority (76.5%) of respondents, were observed to be influenced to major or minor degrees by their desires to prescribe antibiotics for purposes of preventing anticipated infections as sequelae to treated cases (Table 4.12) Being influenced by a factor to any degree can be interpreted as a predisposition of a prescriber to prescribe an antibiotic under the influence of that factor. On the basis of this interpretation, it can

be assumed that the percentage majorities of respondents' results depicted as being influenced to prescribe antibiotics by their desire to eliminate possible infections or prevent anticipated infections, were disposed to prescribe and would prescribe antibiotics for these reasons. The large percentage proportions of respondents observed to be disposed to prescribing antibiotics under the influence of these indicated prescriber- related factors denote significantly that antibiotics are mostly inappropriately prescribed among the study population of prescribers as result of their prescribing behaviour that stemmed from their desire to treat possible or non- existent infections.

Appropriate or judicious use of antibiotics as entailed in the definition of Gaur and English (2006:343) and World Health Organization (2001:1) referred to in earlier paragraphs requires that antibiotics be prescribed for conditions for which they are indicated. Appropriate use of antibiotics in the treatment of infections by this definition necessarily demands that they should be prescribed for appropriately diagnosed infections.

Prescribing antibiotics for possible infections or for preventing anticipated infections as respondents indicated they did, is inappropriate. From results of prescription analysis carried out in study Phase I, 19.2%, of inpatient prescriptions assessed were seen to be appropriately prescribed for absolute bacterial infections (percentage sum total of category A1 and category C prescriptions; Table 4.1.1). Similarly, of the total outpatient prescriptions assessed for their appropriateness 34.6% were found to be appropriately prescribed (sum of category A1 and category C prescriptions out of total outpatient prescriptions assessed Figure 4.1.8) Category A2 prescriptions on the basis of their being prescribed for possible infections were inappropriately prescribed when classified in accordance with definitions of appropriately prescribed antibiotics as provided by Gaur and English (2006: 343) or WHO Global Strategy for Containment of Antimicrobial Resistance (World Health Organization, 2001:1). Re-classifying category A2 prescriptions this way would give a prescription assessment result in research Phase I showing up to 80.8% and 65.4% of inpatient and outpatient prescriptions analysed as being inappropriately prescribed. This evidences a high degree of inappropriate prescribing of antibiotics by the study population of prescribers in both inpatient and outpatient departments. Many of the factors investigated in this study and which were found to have negative impact on appropriateness of antibiotic prescriptions contribute to

this. Nevertheless, and on account of the comparatively large percentage of prescriptions categorised as A2 in research Phase I, prescribers' desire to prescribe antibiotics for possible infections or to prevent anticipated infections are documented as being highly accountable for inappropriate prescribing of antibiotics, particularly in outpatient settings.

- **Prescribers' past experiences as determining factors in their decisions to prescribe antibiotics**

Infections with similar clinical symptoms can be caused by different types or classes of bacteria with different characteristics and hence different propensities to killing by given antibiotics. By implication, this means that an infection that has been diagnosed and successfully treated with a given antibiotic in the past may not necessarily be treated successfully with the same antibiotics upon a second encounter since bacterial pathogens causing the infection the second time around may be different with different antibiotic sensitivity patterns. In line with this thought, it does seem imperative and in accordance with principles of antibiotic prescribing that every infection that is treated should be evaluated in its own merit to establish causative pathogens and their antibiotic sensitivity characteristics. Considered this way, prescribers' past experiences with diagnosed cases and treatment of infections, though they may provide guidelines to the diagnoses of current infections, may not solely be dependent on similar antibiotics for appropriate treatment of infections. Results of investigations into the extent to which prescribers are influenced by their past experiences to prescribe antibiotics in this study showed that more than half of the total number of respondents greatly depended on their past experiences to prescribe antibiotics. A majority (82.3%) by these results do utilise such experiences to a major or minor extent in the treatment of infections (Table 4.3.13). This suggests a disposition towards inappropriate prescribing of antibiotics among the study population of prescribers if the above discussion points are validated.

The association of specific types of bacterial pathogens with infections at given anatomical sites of the body enables the identification and determination of antibiotic sensitivity characteristics of pathogens most probably involved in given infections (Guglielmo, 2008: 56-1) to allow for appropriate selection of antibiotics in the empiric treatment of infections. Prescribers' conversance with such infections and their modes of antibiotic selection for their effective treatment, in the opinion of the researcher, would

depend on what knowledge they accumulate over time on types of bacterial pathogens commonly isolated from sites of such infections and the antibiotic sensitivity patterns of indicated bacterial isolates within the geographical areas of prescribers' practice sites. Viewed from this perspective, respondents' past experiences are envisaged to improve their antibiotic prescribing capabilities and the utilisation of such experiences to a major or minor extent as indications of majority (82.3%) (n = 42) of respondents stipulated, seen as having a positive impact on appropriate antibiotic prescribing.

The effect that prescribers' dependence on their past experiences in treating infections may possibly have on their ability to judiciously prescribe antibiotics as presented above are seen on one hand as contributing to inappropriate and on the other hand as favourable to appropriate prescribing of antibiotics. Some studies designed to demonstrate the impact of prescribers' past experiences on their abilities to prescribe antibiotics appropriately like those exemplified below, did not establish any positive correlation between the two variables. Cadieux *et al.* (2007:881) in one such investigation in which they expressed prescribers' past experiences in treating infections in terms of time spent in practice, showed that inappropriate prescribing of antibiotics actually increased with time prescribers spent in practice. This indicated a negative impact of length of experience on appropriateness of antibiotic prescribing. Gaur *et al.* (2005:635) similarly conducted a study in which they evaluated the differences in overuse of antibiotics among staff physicians and resident/interns who worked in hospital-based outpatient clinics. Staff physicians by their study design; belong to the group of study subjects with experience while the trainees belonged to the group with little or no experience. From results of this study they concluded that, inappropriate prescribing of antibiotics for viral respiratory tract infections occurs more commonly among staff physicians than in trainees. The findings of Gaur *et al.* (2005:635) can be interpreted to mean that prescribers' past experiences in treating infections do not necessarily improve their ability to prescribe antibiotics appropriately. The factor as seen from the results of the study by Cardieux *et al.* (2007:881) may, in fact, contribute to inappropriate prescribing of antibiotics. For more precise determination of what effect prescribers' past experiences in treating infections may have on their ability to prescribe antibiotics appropriately, it is recommended that further studies be done to evaluate prescribers' past experiences and the extent to which they demonstrate such experiences in practice as they prescribe antibiotics.

4.3.3 Determining the extent to which respondents prescribe antibiotics only after positively establishing the presence of infections (Question 10)

The section presents results of investigation into the question of how often prescribers establish the presence of an infection in outpatient settings before prescribing antibiotics. Questions addressed included

- how often respondents would prescribe antibiotics on suspicion of an infection;
- how often they do this only upon patient examination or after laboratory investigations have established the presence of infection; and
- how often they would prescribe antibiotics even if they were not sure of the presence of an infection.

4.3.3.1 Results

Tables 4.3.14 through 4.3.17 show percentage frequency distributions of respondents by qualification and according to their responses to questions seeking to establish the extent to which they prescribe antibiotics following absolute diagnosis of infections in the patient in outpatient settings. Tables 4.3.18(a) and 4.3.18(b) provide analysis of respondents' responses to show what percentages of them would prescribe antibiotics on the basis of either suspicion or absolute establishment of infections as well as probability determinations indicating chances of antibiotic prescriptions being written either without establishing presence of infections or written based on presence of infections.

- **Prescribing antibiotics on suspicion of presence of infections [Question 10(i)].**
  - Of the total number of respondents, 58.8% (n=30) indicated they **always** prescribed antibiotics when they suspected the presence of infections. They consisted of 72.7% (8 out of 11) of physician specialists, 33.3% (1 out of 3) of surgical consultants, 60.0% (15 out of 25) of general practitioners and 37.5% (3 out of 8) nurse clinicians. This is against 39.2% (n=20) who said they

Table 4.3.14 Frequency distributions of respondents by qualification and indications of how often they prescribe antibiotics in outpatient settings on suspicion of presence of infection (Question 10(i)

Response indications	Frequencies of respondents by qualifications and according to indications of how often they prescribe antibiotics in outpatient settings on suspicion presence of infection													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	N%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
Never	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Sometimes	3	27.3	1	33.3	10	40.0	5	62.5	0	0.0	1	50	20	39.2
Always	8	72.7	1	33.3	15	60.0	3	37.5	2	100	1	50	30	58.8
No response	0	0.0	1	33.3	0	0.0	0	0.0	0	0.0	0	0.0	1	2.0
Total	**11**	**100**	**3.0**	**100**	**25**	**100**	**8**	**100**	**2**	**100**	**2**	**100**	**51**	**100**

Table 4.3.15 Frequency distributions of respondents by qualification and indications of how often they prescribe antibiotics in outpatient settings only after they positively establish presence of infection following patient examination (Question 10(ii)

Response indications	Frequencies of respondents by qualifications and according to indications of how often they prescribe antibiotics in outpatient settings only after they positively establish presence of infection through patient examination													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	N%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
Never	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Sometimes	2	18.2	1	33.3	7	28.0	2	25.0	1	50	1	50	14	27.5
Always	9	81.8	1	33.3	18	72.0	6	75.0	1	50	1	50	36	70.6
No response	0	0.0	1	33.3	0	0.0	0	0.0	0	0.0	0	0.0	1	2.0
Total	**11**	**100**	**3.0**	**100**	**25**	**100**	**8**	**100**	**2**	**100**	**2**	**100**	**51**	**100**

prescribed antibiotics **sometimes** only on the basis of their suspicion of infections.

- No respondent denied ever prescribing antibiotics on the basis of suspecting the presence of infections as causes of treated clinical conditions.
- By indicated percentage frequency distributions, physician specialists, followed in that order by general practitioners, nurse clinicians and surgical consultants were observed to be most inclined towards prescribing antibiotics on suspicion of infections.

- **Prescribing antibiotics after absolute establishment of presence of infections following patient examination [Question 10(ii)]**
  - Of the total number of respondents, 70.6% (n=37) and 27.5% (n=13) respectively would **always** and **sometimes**, prescribe antibiotics only following patient examination to ascertain presence of infection.
  - All respondents with the exception of one (1) surgical consultant who did not respond to the question would at one time or the other, prescribe antibiotics only after patient examination to ascertain presence of infection.

- **Prescribing antibiotics only after establishing presence of infections following laboratory investigations [Question 10(iii)]**
  - The percentage of respondents with laboratory facilities and **who are able** to use laboratory assisted information in infection diagnosis and in prescribing antibiotics was 70.6% (n = 36).

Of the total number of respondents (n = 36) with laboratory facilities and who treat patients within outpatient settings,

- 16.7% indicated that they **never** prescribed antibiotics only after establishing presence of infections following laboratory investigations;
- 58.3% (21 out of 36) indicated that they prescribed antibiotics **sometimes** only after laboratory investigations have established presence of infections;
- 25.0% indicated prescribing antibiotics **always** only after laboratory investigations have confirmed presence of infections.

Table 4.3.16 Frequency distributions of respondents by qualification and indications of how often they prescribe antibiotics in outpatient settings only after laboratory investigations establish the presence of infection (Question 10(iii))

Response indications	Frequencies of respondents by qualifications and according to indications of how often they prescribe antibiotics in outpatient settings only after laboratory investigations establish the presence of infection													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
Never	0	0.0 (0.0)	0	0.0 (0.0)	6	24.0 (27.3)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	6	11.8 [16.7]
Sometimes	9	81.8 (81.8)	1	33.3 (33.3)	11	44.0 (50.0)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	21	41.2 [58.3]
Always	2	18.2 (18.2)	1	33.3	5	20.0 (22.7)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	9	17.6 [25.0]
No response	0	0.0 (0.0)	1	(33.3)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	1	2.0 [3.0]
Subtotal (Laboratory facility available	**11**	**(100)**	**3**	**(100)**	**22**	**(100)**	0	0.0 (0.0)	0	0.0 (0.0)	0	0.0 (0.0)	**36**	**70.6 [100]**
Not applicable	0	0.0	0	0.0	3	12.0	8	100	2	100	2	100	15	29.4
Total	**11**	**100**	**3.0**	**100**	**25**	**100**	**8**	**100**	**2**	**100**	**2**	**100**	**51**	**100**

Notation: Percentage calculations in square brackets based on totals of respondents (36) with laboratory facilities
Percentage calculations in round brackets based on subtotals of respondents with laboratory facilities
Percentage calculations without brackets based on column totals of respondents (36) with laboratory facilities

Table 4.3.17 Frequency distributions of respondents by qualification and indications of how often they prescribe antibiotics in outpatient settings even if they are not sure of their diagnosis (Question 10(iv))

Response indications	Frequencies of respondents by qualifications and according to indications of how often they prescribe antibiotics in outpatient settings even if they are not sure of their diagnoses.													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	n%	n	n%	N	n%	n	n%	n	n%	n	n%	n	n%
Never	5	45.5	1	33.3	13	52.0	3	37.5	1	50.0	0	0.0	23	45.1
Sometimes	5	45.5	1	33.3	12	48.0	4	50.0	1	50.0	2	100	25	49.0
Always	1	9.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	2.0
No response	0	0.0	1	33.3	0	0.0	1	12.5	0	0.0	0	0.0	2	3.9
Not applicable	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Total	**11**	**100**	**3.0**	**100**	**25**	**100**	**8**	**100**	**2**	**100**	**2**	**100**	**51**	**100**

- **Prescribing antibiotics even if prescribers are not sure of their diagnoses [Question 10(iv)]**

  - Of the total number of respondents, 41.5% (n = 23) indicated that they **never** prescribed antibiotics when they were not sure of their diagnoses.
  - Respondents indicating that they prescribe antibiotics **sometimes** when they were not sure of their diagnosis constituted 49.0% (n = 25) of the total number of respondents.
  - Of the total number of respondents, 2% (n = 1) composed of 9.1% (1 out of 11) of physician specialists only indicated prescribing antibiotics **always** even if they were not sure of their diagnosis.

- **Predictions of patterns of antibiotic prescribing for suspected or established infections**

  - Of the total number of respondents 98.0% (n = 50) would prescribe antibiotics for suspected infections based on clinical signs and symptoms while 51.0% (n =26) would do the same in cases where they were not sure of their diagnosis.
  - Probability or chances of respondents prescribing antibiotics without establishing presence of infections or prescribing antibiotics by their dependence either on presenting signs and symptoms of treated cases or results of inconclusive diagnosis equalled 0.50 or 50%
  - Of the total number of respondents 70.6% (n = 36) would prescribe antibiotics only if the presence of infection was established after patient examination while 58.8% (n = 30) would similarly do the same if the presence of infection had been established through laboratory investigations.
  - Probability or chances of antibiotics being prescribed based on presence of infection and inferred from results of patient examination and laboratory investigations equalled 0.42 or 42%

Table 4.3.18(a) Percentage frequency distributions of respondents in outpatient settings according to how often they prescribe antibiotics in practice without establishing presence of infection (Question 10)

Statement of how often respondents do what is implied	Number of respondents answering question	Frequency distribution of respondents according to how often they do what statements imply		Chances of respondents prescribing antibiotics ALWAYS and SOMETIMES according to what is implied
		n	n%	
Prescribe antibiotics ALWAYS and SOMETIMES on suspicion of presence of infection based on signs (10.i)	51	50	98.0	0.98
Prescribe antibiotics ALWAYS and SOMETIMES even if not sure of diagnosis (10.iv)	51	26	51.0	0.51

Calculation:
Chances or probability of respondents prescribing antibiotics without establishing presence of infections [$P_{(PAWEPI)}$] based either on clinical signs and symptoms or results of inconclusive diagnosis is given by $P_{(PAWEPI)}$ = [P (10i)] ∩ [P (10iv)] = 0.98 * 0.51 = **0.50**

Table 4.3.18(b) Percentage frequency distributions of respondents in outpatient settings according to how often they prescribe antibiotics in practice without establishing presence of infection (Question 10)

Statement of how often respondents do what is implied	Number of respondents answering question	Frequency distribution of respondents according to how often they do what statements imply		Chances of respondents prescribing antibiotics ALWAYS and SOMETIMES according to what is implied
		n	n%	
Prescribe antibiotics ALWAYS and sometimes only if presence of infection established after patient examination (10.ii)	51	36	70.6	0.71
Prescribe antibiotics ALWAYS and SOMETIMES only after laboratory investigations establish presence of infection (10.iii)	51	30	58.8	0.59

Calculation:
Chances or probability of respondents prescribing antibiotics based on presence of infection [$P_{(PABPI)}$] as determined from results of patient examination or laboratory investigations is given by [$P_{(PABPI)}$] = [P (10ii)] ∩ [P (10iii)] = 0.71 * 0.59 = **0.42**

4.3.3.2 Results evaluation and discussion

Except for their indications as prophylactics in some clinical conditions such as surgical wound prophylaxis or the suppression of infections in categories of patients considered being at risk of those infections, the use of antibiotics in treating clinical cases for which bacterial infections are not established aetiologies is considered inappropriate (Gaur *et al.,* 2006:343). Several disease states e.g. malignancy, autoimmune disease, viral infections or even drug reactions can mimic bacterial infections (Guglielmo, 2008:56-1) and prescribing antibiotics in the management of such conditions in the assumption that they are bacterial infections would be tantamount to the prescription of the drugs for the wrong reasons.

Viewed from the perspective of whether or not they are indicated for clinical conditions for which they are prescribed the assessment of antibiotic prescriptions for their appropriateness provides vital information on the therapeutic benefits derived from the use of the drugs within given clinical environments as against costs incurred, either therapeutic or economic, by their inappropriate prescribing and use. The extent to which prescribers establish the presence of infections before prescribing antibiotics fundamentally determines whether or not antibiotic prescriptions they write would be appropriate when the factor of "indication for treatment" is considered as a criterion in the assessment of antibiotic prescriptions for their appropriateness. In the event of inappropriate antibiotic prescribing being identified as a problem within the clinical environment of origin of assessed prescriptions, it would be possible to associate such problems with shortcomings of prescribers in the diagnosis and treatment of infections to allow for their appropriate redress in attempts to improve antibiotic prescribing within the concerned clinical environment.

Results of study Phase I in which 0.35% (3 out of 865) (Table 4.1.30) only of outpatient antibiotic prescriptions assessed for their appropriateness had shown to be made based on results of laboratory investigations (objective data), established that antibiotic prescribing in outpatient settings is principally done empirically at study sites. Empiric prescribing of antibiotics without prior microbial identification and antibiotic sensitivity determinations is commonly done in medical practice. While in inpatient settings it could be done pending results of microbial investigations of specimens ordered, in outpatient settings it could be the main procedure of antibiotic selection and treatment of many infections as results of Phase I of study showed.

Contributing factors to this in the opinion of the researcher may be inclusive of less serious infections encountered among the patient population group, prescriber high workload and in some cases, the lack of laboratory facilities and/or diagnostic equipment at health service levels where these patients are seen. These factors withstanding, prescribers still do owe it as a duty to responsibly diagnose presenting cases and establish presence of infections as first principle to justify their prescriptions of antibiotics.

Questions asked in the investigation of prescribers' disposition to prescribe antibiotics for suspected or established infections were phrased in ways to enable respondents to differentiate between; and hence indicate appropriately how often they would prescribe antibiotics based on clinical judgements they either make,

- from presenting signs and symptoms without examining the patient or
- from results of diagnostic they undertake to establish presence of infections as questions request.

These were inclusive of physical examination of the patient through which presence and site of infection could be reasonably established or laboratory investigations which could produce objective data needed to confirm presence of infection. Establishing the presence and site of infection according to Guglielmo (2008: 56-1) enables the direction of specific, and hence appropriate, antibiotic therapy against organisms associated with infections present at that site.

The similarities between clinical presentations of certain bacterial and viral infections or bacterial infections and clinical conditions which do not have bacterial aetiologies as indicated above, makes prescribers' dependence on signs and symptoms of disease alone inadequate in justifying most prescriptions of antibiotics they make empirically in treating certain conditions. In a study in which they investigated short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit (ICU), Singh *et al.* (2000:505) disclosed for example that most of the antibiotic use in the ICU occurs in patients in whom pulmonary infiltrates are not caused by pneumonia but rather by pulmonary oedema or atelectasis (*collapse of lung*). They also cited other studies as documenting empiric antibiotic use for ICU patients with pulmonary infiltrates without pneumonia ranging from 34% to 74%. As further evidence of dependence of signs and symptoms alone not being adequate for diagnosis of bacterial infections, notation is made of the assertion of Gonzales *et al.* (2001:492) that purulent secretions from the

nares or throat predict neither bacterial infection nor benefit from antibiotics treatment. According to the authors, when not accompanied by additional predictors of bacterial infection such as illness lasting for seven or more days, purulent nasal discharge and purulent sputum, though relied on by most physicians to assign more specific diagnoses such as rhinosinusitis or acute bronchitis in patients with acute respiratory illness, are weak predictors of bacterial infection in adults with upper respiratory tract infection.

- **The extent of antibiotic prescribing in cases of suspected bacterial infections in outpatient settings**

Inferring from percentage frequencies of their numbers admitting prescribing antibiotics when they suspect infections or when they are not sure of their diagnosis, all qualification categories of respondents can be said to equally demonstrate high tendencies of prescribing antibiotic on the basis of their suspicion of the presence of infections (Table 4.3.17). Physician specialists, by comparative assessment of percentage frequencies of respondent qualifications seen to be prescribing antibiotics on suspicion of the presence of infections, are most often disposed among all qualifications of respondents to prescribing antibiotics on the basis of their suspicion of infections.

All respondents admitted prescribing antibiotics always or sometimes when they suspected infections. On the question of how often respondents prescribed antibiotics when they were not sure of their diagnosis, only 51.0% were seen admitting that they prescribe the drugs always or sometimes when they are not sure of their diagnosis. This difference in the patterns of respondents' responses to the two similar questions can be interpreted only to mean that, respondents find it easier to accept, when asked, that they prescribed antibiotics when they suspected infections than to admit that they prescribed antibiotics even if their diagnoses had not revealed the presence of infections.

- **The extent of antibiotic prescribing only in cases of established infections**

By result indications, 70.6% (n=36) of respondents prescribed antibiotics always only after examining patients to ascertain the presence of infections (Tables 4.3.14) while 58.8% (n = 30) do the same always or sometimes only after establishing the presence of infections following laboratory investigations (Table 4.3.16). Based on practical meanings assigned to responses of "sometimes" to the question of how often respondents prescribe antibiotics only after patient examination or laboratory

investigations (Section 3.5.6), these indicated percentages of respondents are considered to be the proportions of respondents who would prescribe antibiotics for established infections through their respective use of diagnostic procedures involving patient examination and laboratory investigations.

Physician specialists, general practitioners and nurse clinicians, with 81.1%, 72.0% and 75.0% of their numbers respectively indicating that they prescribed antibiotics only after patient examination, are respondent qualifications seen as most disposed to prescribing antibiotics only after examining patients. Surgical consultants appeared to be least disposed to prescribing antibiotics only after examining patients. Except for nurse clinicians who do not have laboratory facilities at their practice sites, the same trend as seen in the case of patient examination is observed in trends of dispositions of respondent qualifications to prescribe antibiotics following laboratory investigations. Unlike surgical consultants who attend to cases of infections involving post-surgical wounds that may be more easily diagnosed from clinical signs and symptoms of infection, physician specialists, general practitioners and nurse clinicians attend to medical cases that most often need diagnostic workups involving patient examination and laboratory investigations to establish the presence of infections before antibiotic treatments are attempted.

- **Predictions of percentage proportions of antibiotic prescriptions written for suspected and established bacterial infection in outpatient settings**

Chances of prescriptions emanating from the outpatient department being written for suspected and absolute infections were determined by following procedures as stipulated in Section 3.3.6 (Methods of data analysis). Forty-two per cent (42.0%) and 50.0% of all antibiotic prescriptions emanating from outpatient departments of study sites by these determinations, are predicted as percentage proportions of antibiotic prescriptions to be written by respondents respectively for established bacterial infections and on suspicion of the presence of such infections [Tables 4.3.18(a) & 4.3.18(b)].

A comparison with results of the analysis of outpatient prescriptions assessed for their appropriateness in study Phase I (Section 4.1.2.1, Table 4.1.24), enabled validation of the percentage outpatient antibiotic prescriptions predicted to be written for suspected and established infections. If classified on the basis of their indications for non-established infections, category A2 prescriptions (n = 378) emanating from outpatient

departments would classify as a category of prescriptions with inappropriately indicated antibiotics. Summed with category B prescriptions (n = 59) which were considered inappropriately written for treatment of infections as many as 437 outpatient prescriptions assessed altogether were seen to be injudiciously written based on their non-indications for established infections. This gives 50.5% of the total prescriptions assessed from outpatient departments of study sites demonstrating as prescriptions inappropriately prescribed on the basis of their being indicated for unconfirmed cases of bacterial infections. The results of Phase I of the study further showed 34.7% of assessed antibiotic prescriptions as prescriptions appropriately written for established bacterial infections.

The 34.7% and 50.5% of assessed antibiotic prescriptions determined as prescriptions given for absolute and suspected infections by comparison, tally adequately with the 42.0% and 50.0% predicted as the prescription types one would expect to be written for established and suspected infections based on determined manners in which respondents indicated their manner of writing antibiotic prescriptions. On the basis of both completed questionnaires and prescriptions analysed for their appropriateness coming from the same study sites and the high possibility that respondents who participated in study Phase III may actually be prescribers responsible for writing most of the prescriptions analysed from outpatient departments, one can consider the tally of actual and predicted percentage prescriptions written for suspected and established infections as reciprocal validations of results of either phase of the study by the other. The tally is also indicative of observed patterns of antibiotic prescribing as established in study Phase I being reflections of antibiotic prescribing behaviours of respondents.

That half of all antibiotic prescriptions originating from outpatient departments of study sites are predicted and actually seen to be antibiotic prescriptions written for suspected infections depict the existence of high chances and proofs of injudicious antibiotic prescribing among outpatient population groups. The manner of antibiotic prescribing as observed is accounted for directly by antibiotic prescribing behaviours of prescribers, a factor documented as a focal area for attention in bids directed towards finding solutions to the problem of injudicious prescription of antibiotics in outpatient departments.

4.3.4 Determining the extent to which respondents adhere to principles of rational prescribing of antibiotics in inpatient settings (Question 11)

Results of the extent to which prescribers adhere to principles of antibiotic prescribing in inpatient settings as investigated are reported in this section. Questions asked principally addressed what prescribers do or are not expected to do in principle in situations of available microbiology laboratory services to ensure appropriate antibiotic treatment of patients diagnosed with infections. They include specifically questions seeking answers to whether or not respondents by principle

- establish morphological characteristics of pathogens before initiation of empiric antibiotic therapy;
- send specimens to microbiology laboratories for culture sensitivity tests before initiating empiric antibiotic therapy; and
- request for culture sensitivity tests only in the event of antibiotic treatment failures or questions seeking to establish how respondents by principle revise antibiotic therapies following their ascertainment of antibiotic sensitivity patterns of infecting bacterial pathogens from results of culture sensitivity tests.

A subset of respondents who treated inpatients and had access to microbiology laboratory facilities only was included in this aspect of the study. Data were analysed to determine the extent to which prescribers adhere to investigated principles as in patient settings.

4.3.4.1 Results

Frequency distributions of respondents by qualifications and according to indications of whether or not they performed listed activities for investigating the extent to which they adhered to antibiotic prescribing principles in inpatient settings were reported in Tables 4.3.19 through 4.3.24 and summarised in outline as presented below.

- **Request for rapid microscopic identification and grams stain properties of pathogens before starting antibiotic treatment [(Question 11(i)]**

  Of the total number (n = 36) of respondents who practised in inpatient settings and had microbiology facilities,

  - 13.8% (n = 5) indicated they did request for rapid microscopic identification of pathogens before starting antibiotic treatment while 36.1% (n = 13) reported doing this at times only, giving a total 50.0% (n = 18) of respondents seen as

characteristically requesting for microscopic identification of infecting bacterial pathogens routinely or at times before prescribing antibiotics;

- 33.3% (n = 12) indicated not requesting for microscopic identification of bacterial pathogens before initiating antibiotic therapy; and
- 11.8% (6 out of 36) did not respond to the question.

- **Sending specimens to a microbiology laboratory for culture sensitivity testing prior to initiation of empiric antibiotic therapy [Question 11(ii)]**

Of a total subset of respondents (n = 36) answering the question,

- 27.8% (n = 10) in each instance of response indicated they sent specimens to laboratories for culture sensitivity tests (CSTs) always or at times before starting empiric antibiotic treatment;
- 55.6% (n = 20) of the respondents were seen as disposed to observing the principle of sending specimens to microbiology laboratories for CSTs before initiating antibiotic treatment in inpatient settings; and
- 30.6% (n = 11) indicated they never requested for culture sensitivity tests before commencing antibiotic therapy in inpatients.

- **Requesting for culture sensitivity tests only in the event of antibiotic treatment failures [Question 11(iii)]**

Of the total subset of respondents (n = 36) to whom the question applied,

- 44.4% (n = 16) and 25.0% (n = 9) indicated they sent specimens to the laboratory for CSTs only in the event of antibiotic treatment failures, always and at times respectively, giving a total 69.4% (n = 25) respondents who were seen to characteristically request for culture sensitivity tests only in the event of antibiotic treatment failures; and
- 13.9% comprising 9.1% (1 out of 11) of physician specialists, 33.3% (1 out of 3) of surgical consultants and 13.6% (3 out of 22) of general practitioners indicated they did not request for culture sensitivity tests only in the event of antibiotic treatment failures.

Table 4.3.19 Frequency distributions of respondents by qualification and indications of whether or not they request for rapid microscopic identification of pathogens prior to prescribing antibiotics for treatment in inpatient settings (Question 11(i))

Response indications	Frequencies of respondents by qualifications and according to indications of requests for rapid microscopic identification of pathogens														
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total		
	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n%
Yes	0	0.0	1	33.3	4	16.0	0	0.0	0	0.0	0	0.0	5	(9.8)	13.8
No	4	36.4	0	0.0	8	36.7	0	0.0	0	0.0	0	0.0	12	(23.5)	33.3
At times	5	45.5	1	33.3	7	31.8	0	0.0	0	0.0	0	0.0	13	(25.5)	36.1
No response	2	18.2	1	33.3	3	13.6	0	0.0	0	0.0	0	0.0	6	(11.8)	16.7
Subtotal (Applicable)	**11**	**100**	**3**	**100**	**22**	**100.0**	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**	**36**	(70.6)	100
Not applicable	0	(0.0)	0	(0.0)	3	(12.0)	8	(100)	2	(100)	2	(100)	15	(29.4)	
Total	**11**	**(100)**	**3.0**	**(100)**	**25**	**(100)**	**8**	**(100)**	**2**	**(100)**	**2**	**(100)**	**51**	**(100)**	

NB: n% without parenthesis based on column totals of subset of respondents to whom question applies
n% with parenthesis based on column totals of all respondents including those to whom question does not apply

Table 4.3.20 Frequency distributions of respondents by qualification and indications of whether or not they send specimens for culture sensitivity tests before initiating empiric antibiotic treatment in inpatient settings (Question 11(ii))

Response indications	Frequencies of respondents by qualifications and according to indications of sending specimens for culture sensitivity tests before initiating empiric antibiotic treatment														
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total		
	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n%
Yes	0	0.0	2	66.7	8	36.4	0	0.0	0	0.0	0	0.0	10	(19.6)	27.8
No	3	27.3	0	0.0	8	36.4	0	0.0	0	0.0	0	0.0	11	(21.6)	30.6
At times	6	54.5	0	0.0	4	18.2	0	0.0	0	0.0	0	0.0	10	(19.6)	27.8
No response	2	18.2	1	33.3	2	9.1	0	0.0	0	0.0	0	0.0	5	(9.8)	13.9
Total (Applicable)	**11**	**100**	**3**	**100**	**22**	**100**	0	0.0	0	0.0	0	0.0	**36**	(70.6)	100
Not applicable	0	(0.0)	0	(0.0)	3	(12)	8	(100)	2	(100)	2	(100)	15	(29.4)	
Total	**11**	**(100)**	**3**	**(100)**	**25**	**(100)**	**8**	**(100)**	**2**	**(100)**	**2**	**(100)**	**51**	**(100)**	

NB: n% without parenthesis based on column totals of subset of respondents to whom question applies
n% with parenthesis based on column totals of all respondents including those to whom question does not apply

Table 4.3.21 Frequency distributions of respondents by qualification and indications of whether or not they send specimens for culture sensitivity tests only after patient non response to initial empiric antibiotic treatment in inpatient settings (Question 11(iii))

Response indications	Frequencies of respondents by qualifications and according to indications of sending specimens for culture sensitivity tests only after patient non response to initial empiric antibiotic treatment														
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total		
	n	n%	N	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n%l applicable(100)
Yes	2	18.2	0	0.0	14	63.7	0	0.0	0	0.0	0	0.0	16	(31.3)	44.4
No	1	9.1	1	33.3	3	13.6	0	0.0	0	0.0	0	0.0	5	(9.8)	13.9
At times	5	45.5	1	33.3	3	13.6	0	0.0	0	0.0	0	0.0	9	(17.6)	25.0
No response	3	27.3	1	33.3	2	9.1	0	0.0	0	0.0	0	0.0	6	(11.8)	16.7
Subtotal (Applicable)	**11**	**100**	**3**	**100**	**22**	**100**	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**	**36**	**(70.6)**	**100**
Not applicable	0	(0.0)	0	(0.0)	3	(12)	8	(100)	2	(100)	2	(100)	15	(29.4)	
Total	**11**	**(100)**	**3**	**(100)**	**25**	**(100)**	**8**	**(100)**	**2**	**(100)**	**2**	**(100)**	**51**	**(100)**	

NB: n% without parenthesis based on column totals of subset of respondents to whom question applies
n% with parenthesis based on column totals of all respondents including those to whom question does not apply

Table 4.3.22 Frequency distributions of respondents by qualification and indications of whether or not they revise antibiotic treatment by discontinuing initially prescribed antibiotics and replacing them with antibiotics to which organisms show sensitivity. [Question 11(iv)]

Response indications	Frequencies of respondents by qualifications and according to indications of revision of antibiotic treatment by replacing initially prescribed antibiotics with antibiotics to which organisms show sensitivity.														
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total		
	n	n%	N	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n/total applicable(100)
Yes	6	54.5	1	33.3	16	72.7	0	0.0	0	0.0	0	0.0	23	(45.1)	63.9
No	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	(0.0)	0.0
At times	3	27.3	1	33.3	2	9.1	0	0.0	0	0.0	0	0.0	6	(11.8)	16.7
No response	2	18.2	1	33.3	4	18.2	0	0.0	0	0.0	0	0.0	7	(13.7)	19.4
Subtotal (Applicable)	**11**	**100**	**3**	**100**	**22**	**100**	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**	**36**	**(70.6)**	**100**
Not applicable	0	0.0	0	0.0	3	12	8	100	2	100	2	100	15	(29.4)	
Total	**11**	**(100)**	**3**	**(100)**	**25**	**(100)**	**8**	**(100)**	**2**	**(100)**	**2**	**(100)**	**51**	**(100)**	

NB: n% without parenthesis based on column totals of subset of respondents to whom question applies
n% with parenthesis based on column totals of all respondents including those to whom question does not apply

Table 4.3.23 Frequency distributions of respondents by qualification and indications of whether or not they revise antibiotic treatment by adding to initially prescribed antibiotics, antibiotics to which organisms are sensitive (Question 11(v))

Response indications	Frequencies of respondents by qualifications and according to indications of revision of antibiotic treatment by adding to initially prescribed antibiotics, antibiotics to which organisms show sensitivity.														
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total		
	n	n%	N	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n%
Yes	2	18.2	0	0.0	9	40.9	0	0.0	0	0.0	0	0.0	11	(21.7)	30.6
No	4	36.4	1	33.3	6	27.3	0	0.0	0	0.0	0	0.0	11	(21.7)	30.6
At times	3	27.3	0	0.0	4	18.2	0	0.0	0	0.0	0	0.0	7	(13.7)	19.4
No response	2	18.2	2	66.7	3	13.6	0	0.0	0	0.0	0	0.0	7	(13.7)	19.4
Subtotal (Applicable)	**11**	**100**	**3**	**100**	**22**	**100**	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**	**36**	**(70.6)**	**100**
Not applicable	0	(0.0)	0	(0.0)	3	(12.)	8	(100)	2	(100)	2	(100)	15	(29.4)	
Total	**11**	**(100)**	**3**	**(100)**	**25**	**(100)**	**8**	**(100)**	**2**	**(100)**	**2**	**(100)**	**51**	**(100)**	

NB: n% without parenthesis based on column totals of subset of respondents to whom question applies
n% with parenthesis based on column totals of all respondents including those to whom question does not apply

- **Revising antibiotic treatment by discontinuing initially prescribed antibiotics and replacing with antibiotics to which organisms are sensitive [Question 11(v)]**

  Of the total subset of respondents (n = 36) to whom the question applied,

  - 63.9% (n = 23) indicated they discontinue always initially prescribed antibiotics and replaced them for antibiotics to which organisms were sensitive while 16.7% (n = 6)) indicated they did this only at times;
  - none indicated ever discontinuing initially prescribed antibiotics and replacing them for antibiotics to which organisms showed sensitivity; and
  - 19.4% (n = 7) did not respond to the question.

- **Revising antibiotic treatment by adding antibiotics to which organisms are sensitive to initially prescribed antibiotics [Question 11(vi)]**

  Of the total subset of respondents (n = 36) to whom the question applied,

  - 30.6% (n = 11) indicated they never added to initially prescribed antibiotics as they revised initial antibiotic treatments with antibiotics to which organisms were sensitive;
  - 30.6% (n = 11) of respondents indicated they did add to initially prescribed antibiotics always and at times antibiotics to which organisms were sensitive as they revised initially prescribed antibiotic treatments;
  - 50.0% (n = 18) were seen indicating they always and at times added to initially prescribed antibiotics, antibiotics to which organisms were reported sensitive from results of CSTs; and
  - 19.4% (n = 7) did not respond to the question.

Table 4.3.24 Frequency distributions of respondents in inpatient settings with laboratory facilities according to how often they observe or violate principles of antibiotic prescribing. (Question 11)

Investigated principles of antibiotic prescribing	Indications of observance of principle			Indications of violations of principle			No response*		Total
	Responses indicating observance of principles	Frequencies of respondents' observance of indicated		Responses indicating violations of principle	Frequencies of respondents' violation of indicated principles				
		n	n%		n	n%	n	n%	
Request for rapid microscopic identification of pathogens before starting antibiotic treatment (11.i)	YES and AT TIMES	18	50.0	NO	12	33.3	6	16.7	36
Request for culture sensitivity tests (CSTs) before initiating empiric antibiotic therapy (11. ii)	YES and AT TIMES	20	55.6	NO	11	30.6	5	13.9	36
Revise antibiotic treatment by replacing initially prescribed antibiotics for antibiotics to which organisms are sensitive (11.iv)	YES	23	63.9	NO and AT TIMES	6	16.7	7	19.4	36
Request for CSTs only in the event of treatment failure(11.iii)	NO	5	13.9	YES and AT TIMES	25	69.4	6	16.7	36
Revise antibiotic treatment by adding antibiotics to which organisms are sensitive to initially prescribed antibiotics (11.v)	NO	11	30.1	YES and AT TIMES	18	50.0	7	19.4	36
Totals and overall calculated percentage of number of times respondents observe or violate principles of rational antibiotic prescribing		77	42.7		72	40.0	31	17.2	180

* "No response" answers were interpreted as negative responses to questions. A respondent refusing to answer a question on an investigated principle is taken as he or she not knowing what to do with respect to observance to that statement of principle.

- **Results summary: The extent of respondents' observance or violation of principles of antibiotic prescribing (Question 11)**

By interpretations given to respondents' answers to questions as provided in Section 3.6.6.1.2 (iv) and summarised in Table 4.3.24 the following percentages of subset of respondents who prescribed antibiotics in inpatient settings could be determined and is reported as the extent to which respondents observed principles of antibiotic treatment of inpatients under circumstances of the availability of microbiology laboratory facilities.

Of the total subset of respondents (n = 36) to which the survey questions applied,

- 50% as against 16.7% observed principles of antibiotic prescribing by requesting for rapid microscopic identification of pathogens before starting antibiotic treatment;
- 55.5% as against 30.6% observed principles of antibiotic prescribing by requesting for culture sensitivity tests before initiating empiric antibiotic therapy;
- 13.9% as against 69.4% observed principles of antibiotic prescribing by not requesting for culture sensitivity tests to be performed only after initial empiric treatment has failed;.
- 63.9% as against 16.7% observed principles of antibiotic prescribing by replacing initially prescribed antibiotics with antibiotics to which organisms were sensitive following availability of expected culture sensitivity test results as they revised their initial empiric antibiotic treatments;
- 30.1% as against 50% (n = 18) observed principles of antibiotic prescribing by not adding to initially prescribed antibiotics, antibiotics to which organisms were sensitive following availability of expected culture sensitivity test results as they revised their initial empiric antibiotic treatments;
- 42.7% (77 out of 180) of the subset of respondents on the average observed principles of antibiotic prescribing when they prescribed antibiotics; and
- 57.2% (103 out of 180) of the subset of respondents comprising 40.0% (72 out of 180) of subset of respondents whose responses indicated they violated the principles and 17.2% (31 out 180) who did not answer questions on indicated principles of antibiotic prescribing, on the average did not observe antibiotic prescribing principles.

4.3.4.2 Results Evaluation and Discussion

The rationale of interpretations given to responses to questions to indicate whether or not respondents followed the indicated principles of antibiotic prescribing in inpatient settings as they prescribed antibiotics is as outlined in Section 3.5.6.

.

- **Adherence to the principle of rapid microscopic identification of pathogens before starting antibiotic treatment**

Percentage frequency distributions of respondents according to the extent of their observance or violations of indicated principles of prescribing antibiotics as investigated in inpatient settings indicated as many as 50% (n = 18) of their total disposed to adhering to the principle of requesting for information on the morphological characteristics of infecting organisms before prescribing antibiotics (Tables 4.3.19 & 4.3.24). With approximately the same proportion of their total numbers included in the 50.0% of respondents reckoned as adhering to this principle, physician specialists and general practitioners can be considered as observing to equal an extent the principle of seeking to know the identity and morphological characteristics of infecting bacteria before prescribing antibiotics. Two thirds of their number indicated they requested for microscopic identification of pathogens before starting antibiotic treatment and in comparison, surgical consultants can be deemed more disposed than physician specialists and general practitioners, to observing the principle.

Though not investigated in this study possible reasons that could be given to explain surgical consultants' seemingly higher disposition to seeking morphological identification of pathogens prior to antibiotic therapy initiation would be, among others, the easier means of obtaining specimens from patients for laboratory investigations in surgical than in medical settings. Other such reasons could be the high possibility of having almost equal chances of organisms with different morphological characteristics being aetiological agents in infections in surgical settings. Bowler *et al.* (2001:244) acknowledged this when they noted in a review they published on wound microbiology and associated approaches to wound management that, wound colonisation is most frequently polymicrobial, involving numerous microorganisms that are potentially pathogenic. Infected wounds, including those surgically inflicted, are the most common cases of infections managed in surgical departments. The break in the protective epidermal layer of the skin resulting from the infliction of these wounds, provide means

of easy access of various pathogens to sites where these infections occur (Bowler *et al.*, 2001:244). The high chances of any pathogen becoming the causative agent of such infections as mentioned make it rather important in such settings to have confirmed knowledge of the identities and characteristics of infecting bacteria to enable appropriate antibiotics to be selected for prescribing. Except for specimens being easily obtained from external fluids from patients in medical wards (for example urine and sputum specimens and specimens from discharges from external cavities) taking specimens in medical settings for laboratory investigations may involve tapping of fluids from suspected sites of infection in internal organs which, as compared to taking specimens in surgical settings, is more difficult to do. This may negate prescribers' wanting to request for rapid identification of infecting microorganisms prior to their prescribing of antibiotics in these settings. Apart from this many clinical infections seen in medical wards present at sites to which certain classes of bacterial pathogens are associated. In the event of a prescriber having good knowledge of common pathogens involved in infections at such sites it is possible to easily target organisms in empiric prescribing of antibiotics for such infections without necessarily resorting to results of microscopic examinations in the laboratory.

- **Adherence to the principle of taking and sending specimens to the laboratory for culture sensitivity tests before initiating antibiotic therapy**

Patients are admitted to hospitals for proper monitoring of their response to treatment on account of the seriousness of their illnesses. In cases where such illnesses have bacterial infections as aetiologies, the attending doctor has enough time while the patient is on admission to identify the assaulting pathogens and determine their sensitivity patterns to antibiotics to enable an effective treatment of the infection. For reasons of avoiding failing to grow pathogens that might be present as aetiological agents of infection being treated if specimens were taken after antibiotic therapy initiation, it is in principle required to send specimens to the laboratory for culture sensitivity testing of infecting bacteria before antibiotic therapy initiation as elaborated in Section 3.5.6 (Scottish Infections Standards and Strategies Group, 2003:282; Bronska *et al.*, 2006:137; Popa *et al.,* 2009:227). When culture sensitivity test (CST) results become available it is the norm to revise antibiotic prescription rationally by replacing initially prescribed antibiotics for antibiotics to which bacteria isolates are sensitive. Practices in antibiotic prescribing in which prescribers ignore these principles or violate them by

doing the opposite of what is required, give rise to antibiotic prescriptions that have the potential of treatment failures and accompanying increased costs of treatment and hospitalisation.

Results of investigations into the extent to which respondents keep to these principles as they prescribe antibiotics in inpatient settings established that a majority (55.6%) of respondents indicated that they kept to the principle of sending specimens to the laboratory for CSTs before initiating empiric antibiotic therapy while 69.4% said they requested for CSTs only in the event of treatment failure (Table 4.3.24). Respondents' assertions of the extent to which they kept to these principles which together addressed the question of the appropriate time to request for bacterial culture antibiotic sensitivity testing in antibiotic therapy were rather contradictory. With 69.4% of them seen as characteristically requesting for CSTs only after treatment failures one would have expected a much smaller percentage claiming that they sent specimens for CSTs before initiating antibiotic therapy. This noted difference is thought to be due to the collapses of "Yes" and "At times" responses on the Likert scale for the question investigating whether or not respondents requested for CSTs before antibiotic treatment initiation, to make the data more practically relevant. Responses of "At times" contrary to considerations given it to enable its rational collapse with "Yes" on the scale may actually be reflective more of respondents' not requesting for CSTs before antibiotic treatment initiation than their requesting for it for reasons given for the collapse. Without the collapse 27.8% of respondents would have been seen indicating that they observed the principle of requesting for CSTs before antibiotic treatment initiation. This percentage frequency determination complements more adequately the 69.4% of respondents determined as requesting for CSTs only after treatment failures. These evaluations of results as provided established the emergence of the two principles dealing with time to request for CSTs as the most violated among the principles investigated. They depict a trend of antibiotic prescribing in inpatient settings that generally shows inclination of prescribers to inappropriate practices of starting empiric antibiotic treatments on trial and error basis to request for determinations of pathogens' sensitivities to antibiotics only when treatment has failed.

The majority of physician specialists were seen to be implicated in antibiotic prescribing practices that violated the indicated principles dealing with time of taking and sending

specimens to microbiology laboratories for bacteria culturing and antibiotic sensitivity determinations. None of this qualification group of prescribers indicated sending specimens for culture sensitivity determinations routinely before initiating antibiotic therapy while 27.3% categorically denied ever doing this and 54.5% claimed they only did it at times. Similarly, 63.6% of them were seen to admit sending specimens for CSTs routinely or at times only after patients' non-response to their initial empiric antibiotic treatment (Tables 4.3.20 & 4.3.21). The observance of the high rate of non- compliance to principles of antibiotic prescribing by physician specialists is anticipated logically to be a major contributing factor to inappropriate prescribing in medical departments. Supervision of patient management in these wards is a responsibility of physician specialists. The observed failure of the qualification group to adhere to principles of antibiotic prescribing can be equally interpreted as a failure on their part to enforce such an adherence, and hence the appropriate prescribing of the drugs, by the junior staff (general practitioners) they supervise. Surgical consultants, like physician specialists supervise patient management in surgical wards. Unlike the latter however, they are much less seen to violate antibiotic prescribing principles that deal with time of taking and sending specimens to microbiology laboratories for CSTs. The majority of them (66.7%) indicated sending specimens to the laboratory routinely for CSTs before initiating antibiotic treatment. The same percentage majority indicated not sending specimens to the laboratory for CSTs or only after initial antibiotic treatment failure or doing so at times (Table 4.3.20 & 4.3.21). They are we also more disposed than physician specialists to establishing morphological characteristics of infecting bacterial pathogens before initiating antibiotic treatment as earlier mentioned. By these results surgical consultants in comparison with physician specialists had a greater inclination towards observing investigated principles of time of taking and sending specimens to laboratories for CSTs and hence were more likely to prescribe antibiotics more appropriately based on these principles than physician specialists. From this observation it can be speculated that antibiotics may be more appropriately prescribed in surgical than in medical department wards. This speculation is made on the basis of the higher likelihood of surgical consultants providing interventions in cases of inappropriate prescribing of antibiotics by junior colleagues under their supervision than physician specialists. Further studies are needed to prove this.

The indications with regard to the majority of general practitioners (77.3%) that they always and at times sent specimens to the laboratory for CSTs only in the event of initial antibiotic treatment failure (Table 4.3.21) predicted high prevalence of improper antibiotic prescribing in inpatient departments by this qualification of category of respondents. This prediction is further strengthened by indications of approximately a third of general practitioners (36.4%) that they do not request for CSTs before initiating empiric antibiotic therapy as results reported. General practitioners practice both in medical and surgical departments and the effects of this prediction on manners of antibiotic prescribing in either of these departments will be determined by the degree of clinical intervention offered by physician specialists or surgical consultants as they assess the antibiotic treatments of infections of their junior colleagues.

- **Adherence to the principle of revising initial antibiotic therapy following availability of results of culture sensitivity tests**

In the situation of antibiotic prescriptions being revised in accordance with results of culture sensitivity tests, a 63.9% majority of respondents were seen to discontinue initially prescribed antibiotics and replace them for antibiotics to which organisms were sensitive in accordance with principles of antibiotic prescribing principles. Contrary to what one would have expected taking into consideration this result, as many as 50% of respondents composed of physician specialists and general practitioners said they did always or at times, add antibiotics to which organisms were sensitive to initially prescribed antibiotics as they revised antibiotic prescriptions when CST results became available (Tables 4.3.22 & 4.3.23). This practice can be justified only in situations where initially prescribed antibacterial would agents target pathogens that could not be grown by culturing procedures used in growing pathogens that have been cultured and tested. In such situations a prescriber could justifiably retain antibacterial agents initially prescribed by empiric multiple antibiotic therapies to cover such bacteria that could not be cultured. Except for this situation, the practice can hardly be justified and show high propensity to inappropriate antibiotic prescribing in inpatient settings.

The implication of physician specialists and general practitioners in this practice suggests the violation of the principle guiding antibiotic prescription revisions following availability of CST results occurring mainly in medical wards. It provides further evidence

of tendencies of antibiotics being prescribed inappropriately according to principles of antibiotic prescribing more often in medical than in surgical wards.

- **Overall prevalence of observance of principles of rational antibiotic prescribing among inpatients.**

Percentages of respondents determined on the average as adhering to or violating principles of antibiotic prescribing when respondents prescribe antibiotics in inpatient settings were reported respectively as 42.7% and 40.0% when "no response" indications are excluded or 42.7% and 57.2% when they were included on account of reasons provided in Section 3.5.6 (Question 11). By interpretation, they indicated chances or probabilities of antibiotic prescriptions being written appropriately or inappropriately for inpatients according to the extent of respondents' observance of principles of antibiotic prescribing investigated. Expressed in terms of ratios, appropriate to inappropriate antibiotic prescriptions that respondents would write if prescription assessment were to be based on their observance of investigated principles would be 1: 1.33 (42.7 : 57.2) approximately.

Results of analysis of antibiotic prescriptions emanating from inpatient departments of study sites in study Phase I and reported in Section 4.1.1.1 (Table 4.1.1), showed percentage frequencies of 32.2% and 48.0% of prescriptions assessed from these patient settings being appropriately and inappropriately written for the treatment of infections. Procedures employed in the prescription assessment utilised a number of criteria developed from principles of antibiotic prescribing including those investigated at this step of the research. The ratio of appropriately to inappropriately assessed prescriptions as calculated gave 1:1.49 which favourably compares with the predicted ratio of 1:1.33 of appropriately to inappropriately assessed prescriptions respondents would write if such an assessment were to be based on their observance of investigated principles. The inference from this comparison as indicated takes cognisance of the fact that criteria employed in the prescription assessment in study Phase I included other criteria developed from principles other than those investigated at this phase of the study. The agreement between the two sets of ratios of appropriately to inappropriately written or supposedly written prescriptions would have been more accurate if criteria used in the assessment of prescriptions in study Phase I were developed from the same principles as those investigated at this phase of the research. A subset of respondents

studied in this part of the research have their practice sites limited to study site hospitals and are presumably responsible largely for prescribing inpatient antibiotic prescriptions that were analysed in study Phase I. They are also bound to constitute a significantly large majority of respondents who answered questions in the part of the questionnaire analysed to determine percentage of respondents appropriately or inappropriately prescribing antibiotics according to principles of antibiotic prescribing in inpatient departments as investigated. Very significantly, the favourable comparison or correlation between the ratios of the predicted and actual percentages of appropriately and inappropriately written inpatient antibiotic prescriptions as reported can be interpreted as an acceptable mutual validation of either method employed in the conduction of data analysis for the two independent studies.

4.3.5 Assessing prescribers' knowledge in principles of antibiotic selection and prescribing

This section reports results of assessment of prescribers' knowledge in principles of antibiotic selection and prescribing and the impact such knowledge would have on prescribers' ability to prescribe antibiotics appropriately. The assessment was carried out in two steps that involved an analysis of respondents'

- score data compiled from answers they provided to knowledge test questions included in questionnaires;
- answers to selected test questions to establish the extent of their practical applications of knowledge in principles of antibiotic selection and prescribing in specific cases of bacterial pathogen associations with sites of infection and also signs and symptoms of cases of infections they diagnosed and treated routinely; and
- answers to specific test questions to establish the extent to which factors of knowledge of morphological characteristics, antibiotic sensitivity and cost impact on respondents' ability to select antibiotics appropriately in practice;

Results of the analysis in line with the three purposes indicated are reported individually and then collectively evaluated and discussed from a perspective that enabled conclusions to be drawn on the extent to which prescribers' knowledge might be seen as affecting their ability to prescribe antibiotics appropriately.

4.3.5.1 Results

- **Analysis of respondents' score data to establish respondents' levels of knowledge in principles of antibiotic selection and prescribing (Questions 12 - 19)**

Frequencies of respondents' score ranges are shown in Tables 4.3.25 and 4.3.26. Histograms of percentage frequency distributions of respondents' score ranges and their performance ratings according to qualifications are shown in Figures 4.3.2 and 4.3.3.

Of the total number of 51 respondents answering to questionnaires,

- 2.0% (n = 1) comprising one general practitioner, had a test performance score in the range of 80 - 100 and fell in the category of performance rating respondents described as having "very good knowledge" in principles of antibiotic selection and prescribing as tested;
- 13.7% (n = 7) had scores in the range of 60 - 79 and fell in the category of performance rating of respondents described as having "good knowledge" in tested principles of antibiotic selection and prescribing. They comprised 9.1% (1 out of 11) of physician specialists and 24.0% (6 out of 25) of general practitioners;
- 25.5% (n = 13) had scores in the range of 40 - 59 and fell in the category of performance rating of respondents described as having "fair knowledge" in tested principles of antibiotic selection and prescribing. They comprised 45.5% (5 out of 11) of physician specialists and 32.0% (8 out of 25) of general practitioners;
- a majority 35.3% (n = 18) respondents had scores in the range of 21-39 and fell in the category of performance rating of respondents described as having "poor knowledge" in principles of antibiotic selection and prescribing; and
- 23.5% (n = 12) of respondents had scores in the range of 0 - 20% and fell in the category of performance rating of respondents described as having "very poor knowledge" in principles of antibiotic selection and prescribing.
- Shape of the data set of respondents' scores is skewed to the right showing respondents with higher scores more spread out than respondents with lower scores.

Table 4.3.25 Frequencies of respondents' scores in test of knowledge in principles of antibiotic selection and prescribing

Percentage score range and performance Classification		Frequency	Relative or percentage Frequency
0-20	(Very poor knowledge)	12	23.5
21-39	(Poor knowledge)	18	35.3
40 – 59	(Fair knowledge)	13	25.5
60 – 79	(Good knowledge)	7	13.7
80 – 100	(Very good knowledge)	1	2
Total		51	100

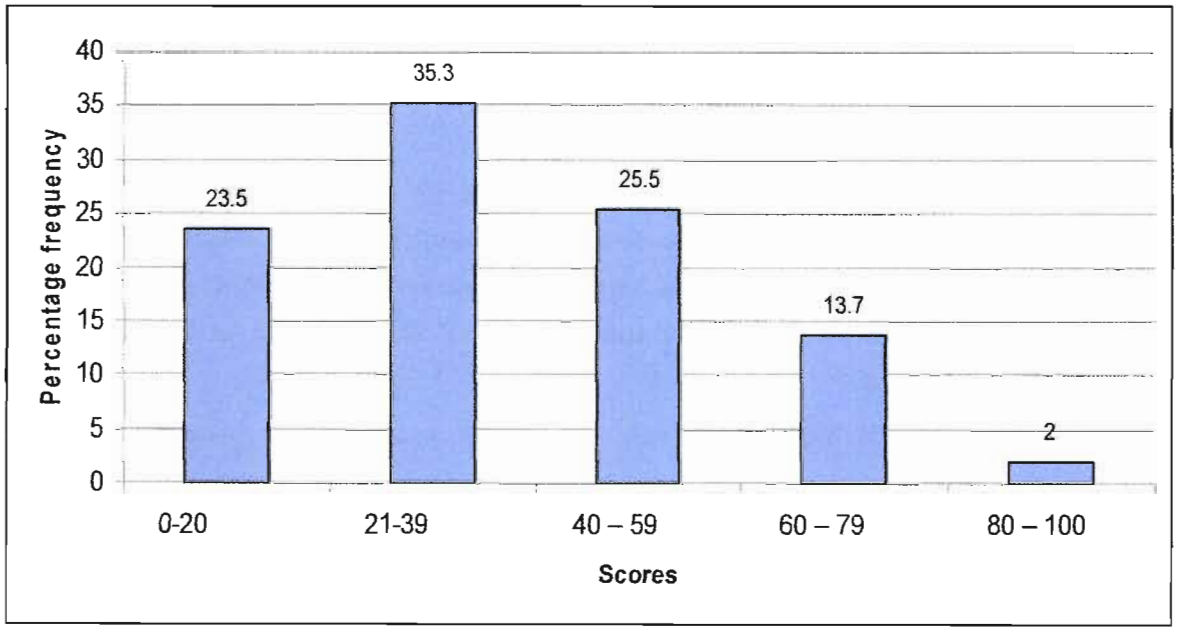

Fig 4.3.2 Respondents' percentage scores in test of knowledge in principles of antibiotic selection and prescribing.

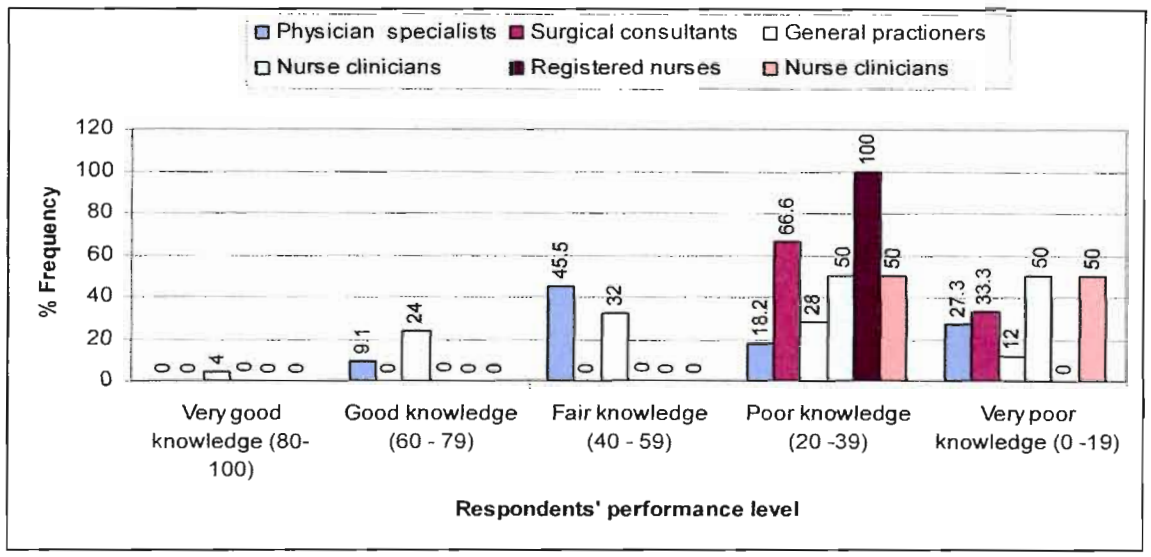

Fig 4.3.3 Percentage frequency distribution of respondents by their qualifications and according to their descriptive performance levels in knowledge test.

Table 4.3.26 Frequency distribution of respondents by qualifications and according to percentage or performance scores and classifications

Response indications to measures taken	Frequencies of respondents by qualifications and according to percentage scores													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
Very good knowledge (80-100)	0	0.0	0	0.0	1	4.0	0	0.0	0	0.0	0	0.0	1	2
Good knowledge (60 -79)	1	9.1	0	0.0	6	24.0	0	0.0	0	0.0	0	0.0	7	13.7
Fair knowledge (40 - 59)	5	45.5	0	0.0	8	32.0	0	0.0	0	0.0	0	0.0	13	25.5
Poor knowledge (20 - 39)	2	18.2	2	66.6	7	28.0	4	50.0	2	100	1	50	18	35.3
Very poor knowledge 0 - 20)	3	27.3	1	33.3	3	12.0	4	50.0	0	0.0	1	50	12	23.5
Total	11	100	3	100	25	100	8	100	2	100	2	100	51	100

- **Assessing respondents' abilities to apply their knowledge in principles of antibiotic prescribing in antibiotic treatments of respiratory and urinary tract infections (Questions 13 and 17)**

Percentage frequency distributions of respondents according their correctness indications of signs and symptoms of bacterial infections of upper and lower respiratory tract and non-sexually transmitted infections of the urinary tract are shown in Tables 4.3.27 through 4.3.39. The following are reported as percentage frequencies of respondents correctly and incorrectly indicating signs and symptoms as indicative of the presence of the given infections.

- **Identification of signs and symptoms associated with upper respiratory tract infections (URTI)**

  .According to respondents' frequencies of indications of signs and symptoms associated with the upper respiratory tract (URT) as shown in Tables 4.3.26 and 4.3.27,

  - 78.4% (n = 40) of the total number of respondents were identified as not being conversant with signs and symptoms necessary to establish bacterial pathogens as aetiological agents in URTI. They included 62.7% (n = 32) of respondents who incorrectly indicated signs and symptoms of infections for URTI and 15.7% (n = 8) who gave no response to the question and hence considered lacking the knowledge;
  - 21.6% (n =11) of the total number of respondents indicated one or more signs and symptoms or diagnoses assessed as being typical of bacterial infections of the upper respiratory tract (URT);
  - no respondent indicated a sign or symptom indicative of bacterial infections of the epiglottis;
  - 29.4% (n = 15) indicated signs and symptoms considered incorrect for diagnosing URTI; and
  - 23.5% (n = 12) cited signs and symptoms not absolute for bacterial infections of the URT.

Table 4.3.27 Frequency distribution of respondents by qualification and according to correctness assessment of stated signs of URTI (Question 13.i)

Assessment	Frequencies of qualifications of respondents according to the correctness of signs and symptoms they indicated as suggesting upper respiratory tract infection.													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	N	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
Correct	2	18.2	0	0.0	9	36.0	0	0.0	0	0.0	0	0.0	11	21.6
Incorrect	7	63.6	0	0.0	14	56.0	7	87.5	2	100	2	100	32	62.7
No response	2	18.2	3	100	2	8.0	1	12.5	0	0.0	0	0.0	8	15.7
Subtotal(Incorrect plus no response)	**9**	**81.8**	**3**	**100**	**16**	**64.0**	**8**	**100**	0	0.0	0	0.0	**40**	**78.4**
Total	**11**	**100**	**3**	**100**	**25**	**100**	**8**	**100**	**2**	**100**	**2**	**100**	**51**	**100**

- **Identification of signs and symptoms associated with lower respiratory tract infections (LRTI)**

  Respondents' identifications of signs and symptoms associated with infections of the lower respiratory tract (LRT), as Tables 4.3.28 and 4.3.29 show, depicted

  - 60.8% (n = 31) of respondents correctly mentioning one or more signs and symptoms commonly associated with bacterial infections of the lower respiratory tract; and
  - 39.2% (n = 20) of respondents either indicated signs and symptoms considered incorrect for establishing bacterial infections of LRT or did not answer the question and hence were considered lacking the knowledge.

- **Identification of signs and symptoms associated urinary tract infections uncomplicated with non-sexually transmitted diseases**

  Percentage frequency distribution of respondents according to their correct or incorrect indications of signs and symptoms of non-sexually transmitted urinary tract infections as reported in Tables 4.3.30 and 4.3.31 indicates that,

  - respondents correctly mentioning signs and symptoms associated with non-sexually transmitted urinary tract infections represent 66.7% (n = 34) of total number of respondents; and

Table 4.3.28 Percentage frequency distribution of respondents according to signs and symptoms indicated for URTI [Question 13(I)]

Sign and symptoms of indicated diagnoses of URTI	Comments on whether or not signs or symptoms indicated or are absolute for bacterial infection of upper respiratory tract.	Frequencies of respondents according to indications of any one of indicated symptoms													
		Physician specialist		Surgical consultant		General practitioner		Nurse clinician		Registered nurse		Nurse assistant		Totals	
		n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
Absolute signs of bacterial infections of upper respiratory tract															
Acute sinusitis: nasal purulence, congestion or cough for >7days, (adults) or for 10-14 days (in childrenn) or focal facial swelling or tooth pain (adults or facial swelling or pain with fever (102°F) (chn) lasting for any length of period	Absolute	0	0	0	0	2	8	0	0	0	0	0	0	2	3.9
Bacterial pharyngitis/ retropharyngeal abscess: Fever, tosilar swelling, exudates, enlarged/tender anterior cervical swelling lymph nodes, dysphagia	Absolute	2	18.2	0	0	4	16	0	0	0	0	0	0	6	11.8
Otitis media: Purulent otorrhoea + Fever, irritability, otalgia, decreased hearing, tinnitus and vertigo	Absolute	0	0	0	0	3	12	0	0	0	0	0	0	3	5.9
Epiglottitis: Enlarged cherry red looking epiglottis with fever, sore throat, tachycardia, inspiratory stridor with muffled voice	Absolute	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Sub total		**2**	**18.2**	**0**	**0**	**9**	**36**	**0**	**0**	**0**	**0**	**0**	**0**	**11**	**21.6**
No indications of signs and symptoms or indicated signs and symptoms neither not indicative or absolute for bacterial infections of upper respiratory tract															
Rhinorrhoea, fever, dry cough, laryngitis, sore throat, generalised malaise, Inflammed tonsils,	Not absolute	1	9.1	0	0	9	36	2	25	0	0	0	0	12	23.5
Dyspnoea, tachypnoea, chest pain, Cough (productive with or without blood stained or coloured sputum, Cough>2weeks, eye discharge, poor appetite	Not bacterial infection of URTI	4	36.4	0	0	4	16	5	62.5	1	50	1	50	15	29.4
No indication of any of the above	No knowledge	4	36.4	3	100	3	12	1	12.5	1	50	1	50	13	25.5
Subtotal		**9**	**81.8**	**3**	**100**	**16**	**64**	**8**	**100**	**2**	**100**	**2**	**100**	**40**	**78.4**
Total		**11**	**100**	**3**	**100**	**25**	**100**	**8**	**100**	**2**	**100**	**2**	**50**	**51**	**100**

Table 4.3.29 Frequency distribution of respondents by qualification and according to correctness assessment of stated signs and symptoms of LRTI (Question 13.ii).

Assessment	Frequencies of respondents by qualifications and according to assessment of stated signs of lower respiratory tract infection.													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
Correct	4	36.6	**0**	**0.0**	20	80.0	4	50.0	2	100	1	50.0	31	60.8
Incorrect	3	27.3	**0**	**0.0**	3	12.0	2	25.0	**0**	**0.0**	0	0.0	8	15.7
No response	4	36.4	3	100	2	8.0	2	25.0	**0**	**0.0**	1	50.0	12	23.5
Subtotal(Incorrect plus no response)	**7**	**63.6**	**3**	**100**	**5**	**20**	**4**	**50.0**	0	0.0	1	50.0	**20**	**39.2**
Total	**11**	**100**	**3**	**100**	**25**	**100**	**8**	**100**	**2**	**100**	**2**	**100**	**51**	**100**

Table 4.3.30: Percentage frequency distribution of respondents according to signs and symptoms indicated for LRTI [Question 13(ii)]

Sign and symptoms of indicated diagnoses of LRTI	Indication of whether absolute for bacterial infection of upper respiratory tract or not	Frequencies of respondents by qualifications and according to indications of any one of indicated symptoms													
		Physician specialist		Surgical consultant		General practitioner		Nurse clinician		Registered nurse		Nurse assistant		Totals	
		n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
Absolute signs of bacterial infections of lower respiratory tract															
Exacerbated Chronic bronchitis: Increased production of purulent sputum	Absolute	1	9.1	0	0	3	12	2	25	1	50	0	0	7	13.7
Pneumonia (Community or Hospital acquired) Fever, tachypnoea, tachycardia, pleuritic (knife like) chest pain, Dullness on chest percussion. Decreased breath sounds, vowel tone changes	Absolute	3	27.3	0	0	17	64	2	25	0	0	0	0	22	43.1
Other infections of lower respiratory tract. Persistent cough with Blood stained sputum,	Absolute	0	0	0	0	0	0	0	0	1	50	1	50	2	3.9
Subtotal		**4**	**36.4**	**0**	**0**	**20**	**80**	**4**	**50**	**1**	**50**	**1**	**50**	**31**	**60.8**
No indications of signs and symptoms or indicated signs and symptoms neither not indicative nor absolute for bacterial infections of the lower respiratory tract															
Shortness of breath, crepitations	Not absolute for bacterial infection of lower respiratory tract.	3	27.3	0	0	2	8.0	1	12.5	0	0	0	0	6	11.8
Persistent dry cough, Chest pain abdominal pain, fever	Not bacterial infection of lower respiratory tract	0	0	0	0	1	4.0	1	12.5	0	0	0	0	2	3.9
No indication of any of the above	No knowledge	4	36.4	3	100	2	8.0	2	25	0	0	1	50	12	23.5
Subtotal		**7**	**63.6**	**3**	**100**	**5**	**20**	**4**	**50**	**0**	**0**	**1**	**50**	**20**	**39.2**
Total		**11**	**100**	**3**	**100**	**25**	**100**	**8**	**100**	**2**	**100**	**2**	**100**	**51**	**100**

Table 4.3.31 Frequency distribution of respondents by qualification and according to correctness assessment of stated signs and symptoms of non-sexually transmitted urinary tract infection (NSTUTI) (Question 13.iii)

Assessment	Frequencies of respondents by qualifications and according to assessment of stated signs of non sexually transmitted urinary tract infection.													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
Correct	6	54.5	**0**	**0.0**	19	76.0	6	75.0	2	100	1	50	34	66.7
Incorrect	2	18.2	**0**	**0.0**	2	8.0	0	0.0	0	0.0	1	50	5	9.8
No response	3	27.3	3	100	4	16.0	2	25.0	0	0.0	0	0.0	12	23.5
Subtotal(Incorrect plus no response)	**5**	**45.5**	**3**	**100**	**6**	**24**	**2**	**25**	0	0.0	1	50	**17**	**33.3**
Total	**11**	**100**	**3**	**100**	**25**	**100**	**8**	**100**	**2**	**100**	**2**	**100**	**51**	**100**

Table 4.3.32: Percentage frequency distribution of respondents according to signs and symptoms indicated for (NSTUTI) [Question 13(iii)]

Sign and symptoms of indicated diagnoses of (NSTUTI)	Indication of whether or not symptom is absolute for bacterial infection of upper respiratory tract or not	Frequencies of respondents by qualifications and according to indications of any one of indicated symptoms													
		Physician specialist		Surgical consultant		General practitioner		Nurse clinician		Registered nurse		Nurse assistant		Totals	
		n	n%	n	n%	N	n%	n	n%	n	n%	n	n%	n	n%
Absolute signs of bacterial infections of lower respiratory tract															
Lower UTI(Cystitis/ Urethritis) Dysuria, frequent urination, suprapubic pain, grossly cloudy urine	Absolute	2	18.2	0	0	11	40	3	37.5	1	50	1	50	18	35.3
Upper UTI(Acute pyelonephritis (pain in the loin, fever chills, vomiting, haematuria) or **Prostatitis** (chills, fever , perineal and lower back pain, urinary urgency and frequency, nocturia, dysuria, generalised malaise**)**,	Absolute	4	36.7	0	0	8	36	3	37.5	1	50	0	0	16	31.4
Subtotal		**6**	**54.5**	**0**	**0**	**19**	**76**	**6**	**75**	**2**	**100**	**1**	**50**	**34**	**66.7**
No indications of signs and symptoms or indicated signs and symptoms neither not indicative or absolute for bacterial infections of upper respiratory tract															
Vaginal / Penile Discharge,	Not absolute for (NSTUTI)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
No indication of any of the above	Lack adequate knowledge	5	45.5	3	100	6	24	2	25	0	0	1	50	17	33.3
Subtotal		**5**	**45.5**	**3**	**100**	**6**	**24**	**2**	**25**	**0**	**0**	**1**	**50**	**17**	**33.3**
Total		**11**	**100**	**3**	**100**	**25**	**100**	**8**	**100**	**2**	**100**	**2**	**100**	**51**	**100**

- respondents incorrectly indicating signs and symptoms of urinary tract infections uncomplicated with sexually transmitted infections or did not answer the questions and were hence considered lacking the knowledge represent 33.3% (n = 17) of the total respondents.

- **Respondents' indications of bacterial pathogens associated with upper respiratory tract infections (URTI)**

Frequencies of indications of bacterial pathogens respondents considered as associated causative agents of infections of the upper respiratory tract (URT) as tabulated in Tables 4.3.32 and 4.3.33 show that,

- 49.0% (n = 25) of the total number of respondents indicated bacterial pathogens known to be commonly implicated in infections of the upper respiratory tract;
- 43.1% (n = 22) out of total 49.0% of respondents indicating bacterial pathogens known to be commonly implicated in infections of the URT mentioned at least one or more of the following pathogens, namely, Streptococci (*S. pyogenes*, *S. pneumoniae), H. influenzae and M. catarrhalis* and are considered having "good knowledge" in their associations of bacterial pathogens with URTIs. These organisms in addition to *Corynebacterium diphtheriae*, *Klebsiella rhinoscleromatis and Klebsiella ozaenae* which rather were not mentioned by any respondent are documented as commonly responsible for bacterial infections of the upper respiratory tract (Section 2.1.5); and
- no respondent in the nursing cadre indicated any pathogen known to be associated with infections of the URT.

Table 4.3.33. Frequency distribution of respondents by qualification and according to correctness assessment of bacterial pathogens stated as being associated with URTI (Question 17.i)

Assessment	Frequencies of respondents by qualifications and according to assessment of stated bacterial pathogens associated with upper respiratory tract infection													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
Correct	5	45.5	1	**33.3**	19	76	0	0.0	0	0.0	0	0.0	25	49.0
Incorrect	2	18.2	0	**0.0**	3	12	4	50	1	50	1	50	11	21.7
No response	4	36.4	2	66.7	3	12	4	50	1	50	1	50	15	29.4
Subtotal(Incorrect plus no response)	**6**	**54.5**	**2**	**66.7**	**6**	**24**	**8**	**100**	**2**	**100**	**2**	**100**	**26**	**51**
Total	**11**	**100**	**3**	**100**	**25**	**100**	**8**	**100**	**2**	**100**	**2**	**100**	**51**	**100**

Table 4.3.34 : Frequency distribution of respondents according to their indications of bacterial pathogens commonly associated with upper respiratory tract infections. [Question 17(i)]

Respondent indicated bacterial pathogens by name or class	Frequencies of respondents by qualifications and according to indications of pathogens													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
Indicated pathogens commonly associated with infection														
Streptococci(S. pyogenes, *S. pneumoniae)*	3	27.2	1	33.3	10	40	0	0	0	0	0	0	14	27.5
Streptococci + H. influenzae	1	9.1	0	0	6	24	0	0	0	0	0	0	7	13.7
H. influenzae + Streptococci + M. catarrhalis	1	9.1	0	0	0	0	0	0	0	0	0	0	1	2.0
Corynebacterium diphtheriae	0		0	0	0	0	0	0	0	0	0	0	0	0.0
Sub Total	**5**	**45.5**	**1**	**33.3**	**16**	**64**	**0**	**0**	**0**	**0**	**0**	**0**	**22**	**43.1**
Indications of mixed types of pathogens commonly and not commonly associated with infection														
Staph. aureus and Streptococci	0	0	0	0	1	4	0	0	0	0	0	0	1	2.0
Staph. aureus, K. pneumoniae and S. pneumoniae	0	0	0	0	1	4	0	0	0	0	0	0	1	2.0
Staph aureus, H. influenzae	0	0	0	0	1	4	0	0	0	0	0	0	1	2.0
Sub Total	**0**	**0**	**0**	**0**	**3**	**12**	**0**	**0**	**0**	**0**	**0**	**0**	**3**	**5.9**
No pathogens indicated or indicated pathogens not commonly associated with infection or not bacteria														
Bacteria (unspecified)	0	0	0	0	1	4	2	25	1	0	1	0	5	9.8
Enterobacteriaceae (too broad)	1	9.1	0	0	0	0	0	0	0	0	0	0	1	2.0
Not bacteria pathogen (Virus)	1	9.1	0	0	0	0	2	25	0	0	0	0	3	5.9
No pathogen indicated	4	36.4	2	0	5	20	4	50	1	0	1	0	17	33.3
Sub total	6	54.5	2	66.7	6	24	8	100	2	100	2	100	26	51.0
Total	**11**	**100**	**3**	**100**	**25**	**100**	**8**	**100**	**2**	**100**	**2**	**100**	**51**	**100**

- The results reveal that 5.9% (n = 3) of respondents indicated mixed pathogens that included *Staphylococcus aureus* and *Klebsiella pneumoniae* which are not ordinarily implicated in infections of the upper respiratory tract together with one or more of the above indicated pathogens known to commonly cause URTIs. They form the percentage of respondents considered having "fair knowledge" of bacterial pathogens implicated in URTIs because of their inability to differentiate pathogens that commonly infect the upper respiratory tract from those that may occasionally be involved in infections at this anatomical site in some patient groups only.
- Fiftty-one per cent (51.0%) (n = 26) of respondents composed of 54.5% (6 out of 11) of physician specialists, 66.67% (2 out of 3) of surgical consultants, 24% (6 out of 24) general practitioners and 100% each of nurse clinicians (8 out of 8), registered nurses (2 out of 2) and nurse assistants (2 out of 2) indicated no pathogens or indicated "viruses" or "bacteria" as their responses to questions asking them to mention bacterial pathogens associated with URTI. They are classified as displaying "very poor knowledge" in bacteriology of upper respiratory tract infections.

- **Respondents' indications of bacterial pathogens associated with Lower respiratory tract infections (LRTI)**

Tables 4.3.34 and 4.3.35 show frequencies of respondents' indications of pathogens they considered as associated with bacterial infections of the lower respiratory tract. Assessments of the correctness of such responses indicated associated bacterial pathogens of the lower respiratory tract (LRT) show that,

- 51.0% (n = 26) of the total number of respondents indicated organisms commonly associated with lower respiratory tract infections;
- 49.1% (n = 25) of respondents correctly indicated one or more of the following pathogens, namely, *Streptococcus* (*S. pneumoniae*) *H. influenzae, Klebsiella pneumoniae Mycoplasma* (community acquired pneumonia), and *Staphylococcus aureus*, *E. coli* (occasionally in hospitalised patients) as pathogens commonly associated with lower respiratory tract infections. They are considered having "good knowledge" of bacterial pathogens most often implicated in LRTI;

- 2.0% (n = 1) of respondents indicated bacteria classes such as *Clamydia*, gram-positive and gram-negative organisms as bacterial pathogens associated with LRTI. No respondent indicated *Moraxella catarrhalis,* and *Pseudomonas aeruginosa* as associated pathogens with lower respiratory tract infections. These pathogens are commonly and respectively associated with community and hospital acquired LRTI; and
- 49.0%(n = 25) of respondents indicated pathogens that are not associated with LRTIs or are uniquely treated with specific drugs other than ordinarily available antibiotics. They are considered having "poor knowledge" in the bacteriology of lower respiratory tract infections.

Table 4.3.35 Frequency distribution of respondents by qualification and according to correctness assessment of stated bacterial pathogens associated with LRTI (Question 17.ii)

Assessment	Frequencies of respondents by qualifications and according to assessment of stated bacterial pathogens associated with lower respiratory tract infection													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	n%	n	n%	n	n%	N	n%	n	n%	n	n%	n	n%
Correct	6	54.5	0	**0.0**	17	68.0	2	25.0	0	0.0	1	50.0	26	51
Incorrect	1	9.1	1	**33.3**	5	20.0	2	25.0	1	50.0	0	0.0	10	19.6
No response	4	36.4	2	66.7	3	12.0	4	50.0	1	50.0	1	50.0	15	29.4
Subtotal(Incorrect plus no response)	**5**	**45.5**	**3**	**100**	**8**	**32.0**	**6**	**75.0**	**2**	**100**	**2**	**100**	**25**	**49**
Total	**11**	**100**	**3**	**100**	**25**	**100**	**8**	**100**	**2**	**100**	**2**	**100**	**51**	**100**

Table 4.3.36 Frequency distribution of respondents according to their indications of bacterial pathogens commonly associated with lower respiratory tract infections.[(Question 17(ii)]

Respondent indicated bacterial pathogens by name or class	Frequencies of respondents by qualifications and according to indications of pathogens													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
Indicated pathogens commonly and occasionally associated with lower respiratory tract infection														
Streptococcus (S. pneumoniae)	1	9.1	0	0	5	20	2	25	0	0	0	0	8	15.7
Streptococcus + H. influenzae	1	9.1	0	0	3	12	0	0	0	0	0	0	4	7.8
Streptococcus + H. influenzae +Klebsiella	0	0	0	0	2	8	0	0	0	0	0	0	2	3.9
Moraxella catarrhalis (Gram –ve cocci)	0	0	0	0	0	0	0	0	0	0	0	0	0	0.0
Staphylococcus	0	0	0	0	0	0	0	0	0	0	1	0	1	2.0
Staphylococcus+ Mycobacterium	0	0	0	0	1	4	0	0	0	0	0	0	1	2.0
Streptococcus + Staphylococcus	1	9.1	0	0	0	0	0	0	0	0	0	0	1	2.0
Streptococcus + Staphylococcus +Mycobacterium	1	9.1	0	0	1	4	0	0	0	0	0	0	2	3.9
Streptococcus + Staphylococcus +H. influenzae	0	0	0	0	1	4	0	0	0	0	0	0	1	2
Streptococcus + Staphylococcus + H. Influenza Mycoplasma, Klebsiella	1	9.1	0	0	1	4	0	0	0	0	0	0	2	3.9
S. pneumoniae, H. Influenzae, E. Coli	0	0	0	0	1	4	0	0	0	0	0	0	1	2.0
Gram +ve and Gram –ve cocci	1	9.1	0	0	0	0	0	0	0	0	0	0	1	2.0
Gram +ve cocci, facultative anaerobic bacilli, Gram -ve aerobic coccobacilli	0	0	0	0	1	4	0	0	0	0	0	0	1	2.0
Sub Total	**6**	**54.5**	**0**	**0**	**16**	**64**	**2**	**25**	**0**	**0**	**1**	**50**	**25**	**49.1**
Indications of mixed types of pathogens commonly and not commonly or occasionally associated with infection														
Clamydia + Gram-positive and Gram negative	0	0	0	0	1	4	0	0	0	0	0	0	1	2.0
Sub Total	**0**	**0**	**0**	**0**	**1**	**4**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**2.0**
No pathogens indicated or indicated pathogens unspecified or are uniquely treated with specific drugs														
Bacteria (unspecified)	0	0	1	33.3	0	0	1	12.5	1	50	0	0	3	5.9
Gram+ve and Gram +ve (vague)	1	9.1	0	0	2	8	0	0	0	0	0	0	3	5.9
Mycobacterium	0	0	0	0	2	8	0	0	0	0	0	0	2	3.9
No pathogens indicated	4	36.4	2	66.7	4	16	5	62.5	1	50	1	50	17	33.3
Sub total	5	45.5	3	100	8	32	6	75.0	2	100	1	50	25	49.0
Total	**11**	**100**	**3**	**100**	**25**	**100**	**8**	**100**	**2**	**100**	**2**	**100**	**51**	**100**

- **Respondents' indications of bacterial pathogens associated with urinary tract infections uncomplicated with sexually transmitted diseases**

Frequencies of respondents' indications of pathogens they considered associated with non-sexually transmitted urinary tract infection (NSTUTI) are shown in Tables 4.3.6 and 4.3.37. Analysis of the tabulated data indicated that;

- 41.2% (n = 21) of respondents mentioned bacterial pathogens considered commonly or occasionally associated with the infection NSTUTI.
- 31.3 % (n= 16) of respondents are considered having "good knowledge" in bacteriology of NSTUTI by mentioning *E. coli*, *Klebsiella* spp, *Proteus* spp, *Pseudomonas* spp, or Gram-negative bacilli in some cases as commonly and occasionally associated bacterial pathogens with NSTUTI;
- 9.8% of respondents are considered having "fair knowledge" in bacteriology of non-sexually transmitted urinary tract infections by listing mixed pathogens that are commonly and not commonly associated with NSTUTI; and
- 58.8% respondents are considered having "poor knowledge" in bacteriology of NSTUTI by indicating no pathogens, or indicating pathogens not associated with NSTUTI or vaguely indicating "bacteria" classified by gram staining characteristics.

Table 4.3.37 Frequency distribution of respondents by qualification and according to correctness assessment of stated bacterial pathogens associated with NSTUTI (Question 17.iii)

Assessment	Frequencies of respondents by qualifications and according to assessment of stated bacterial pathogens associated with non-sexually transmitted urinary tract infection													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
Correct	5	45.5	1	**33.3**	15	64.0	0	0.0	0	0.0	0	0.0	21	41.2
Incorrect	2	18.2	0	**0.0**	5	20.0	3	37.5	1	50.0	1	50.0	12	23.5
No response	4	36.4	2	66.7	5	20.0	5	62.5	1	50.0	1	50.0	18	35.3
Subtotal(Incorrect plus no response)	**6**	**54.5**	**2**	**66.7**	**13**	**40**	**8**	**100**	**2**	**100**	**2**	**100**	**30**	**58.8**
Total	**11**	**100**	**3**	**100**	**25**	**100**	**8**	**100**	**2**	**100**	**2**	**100**	**51**	**100**

Table 4.3.38 Frequency distribution of respondents according to their indications of bacterial pathogens commonly associated with urinary tract infections [Question 17 (iii)]

Respondent indicated bacterial pathogens by name or class	Frequencies of respondents by qualifications and according to indications of pathogens													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
Pathogens commonly and occasionally associated with infection														
E. coli	3	27.3	0	0	7	28	0	0	0	0	0	0	10	19.6
E.coli, Klebsiella spp	0	0	1	33.3	0	0	0	0	0	0	0	0	1	2
E.coli, *Proteus* spp,	1	9.1	0	0	0	0	0	0	0	0	0	0	1	2
Enterobacter	0	0	0	0	2	8	0	0	0	0	0	0	2	4
E.coli + *Pseudomonas* spp	0	0	0	0	1	4	0	0	0	0	0	0	1	2
E. coli, *Proteus* spp, Enterobacter, *Enterococcus*	0	0	0	0	1	4	0	0	0	0	0	0	1	2
Subtotal	4	36.4	1	33.3	11	44	0	0	0	0	0	0	16	31.3
Indications of mixed types of pathogens commonly and not commonly associated with infection														
E coli + *Shigella*	1	9.1	0	0	0	0	0	0	0	0	0	0	1	2
E.coli +*Staphylococcus*	0	0	0	0	2	8	0	0	0	0	0	0	2	4
Klebsiella spp., *Staphylococcus*, fungi, non-Haem streptococcus	0	0	0	0	1	4	0	0	0	0	0	0	1	2
E. coli, P. mirabilis, Klebsiella, Enterococus, Staph saprophyticus, S. epidimidis	0	0	0	0	1	4	0	0	0	0	0	0	1	2
Subtotal	1	9.1	0	0	4	16	0	0	0	0	0	0	5	9.8
No pathogens indicated/ indicated pathogens unspecified / indicated pathogens not associated with infection														
Bacteria (unspecified)	0	0	0	0	1	4	1	12.5	1	50	0	0	3	5.9
Gram -ve and Gram +ve (vague)	2	18.2	0	0	1	4	0	0	0	0	0	0	3	5.9
Clamydia trachomatis	0	0	0	0	1	4	0	0	0	0	0	0	1	2
Streptococcus	0	0	0	0	0	0	1	12.5	0	0	0	0	1	2
Salmonella	0	0	0	0	0	0	0	0	0	0	1	50	1	2
No pathogens indicated	4	36.4	2	66.7	7	28	6	75	1	50	1	50	21	41.2
Subtotal	6	54.5	2	66.7	10	40	8	100	2	100	2	100	30	58.8
Total	11	100	3	100	25	100	8	100	2	100	2	100	51	100

- **Determining the extent to which factors of knowledge of morphological characteristics bacterial pathogens influence respondents' selection of antibiotics in specified clinical scenarios (Questions 18, 19)**

Percentage frequency distributions of respondents according to their indications of preferred antibiotics selected from given lists of antibiotics, namely, ampicillin, co-trimoxazole and cefotaxime, in the treatment of gram-positive cocci and gram-negative bacilli infections of surgical wounds, are shown in Tables 4.3.39 and 4.3.40. and outlined below. Theoretical basis of making antibiotic choices are provided in Appendix 15.

- **Antibiotic selection in treating gram-positive cocci infections of surgical wounds**

Of a total number of 51 respondents,

- 2% (n= 1) correctly selected co-trimoxazole over ampicillin and cefotaxime based on the antibiotics' spectrum of activity against gram-positive cocci organisms and cost considerations as discussed in marking scheme;
- 98.0% (n=50) did not select co-trimoxazole and were deemed lacking the knowledge on spectra of activities and costs of listed antibiotics as discussed in marking scheme and which in principle should be used in the selection process;
- ampicillin was selected rather than co-trimoxazole and cefotaxime by 39.2% (n = 20) of respondents;
- cefotaxime was selected rather than ampicillin and co-trimoxazole by 21.6% (n = 11) of respondents; and
- 37.3% (n = 19) of respondents admitted lack of the tested knowledge by indicating that they were not sure of which antibiotic to select from among the three listed antibiotics.

- **Antibiotic selection in treating gram-negative bacilli infections of surgical wounds**

Of total number of 51 respondents,

- 43.1% (n = 22) correctly selected cefotaxime rather than co-trimoxazole and ampicillin and presumably are in the knowledge of the show of activity of cefotaxime in contrast to co-trimoxazole and ampicillin against *Pseudomonas;*

Table 4.3.39: Frequency distribution of respondents according to their indications of antibiotics of choice in gram-positive cocci infections of surgical wound. (Question 18)

Antibiotic selection options	Frequencies of respondents by qualifications and according to indications of antibiotics of choice													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	n%	n	n%	n	n%	n	n%	n	n%	N	n%	n	n%
Ampicillin	4	36.4	0	0	12	48	1	12.5	2	100	1	50	20	39.2
Co-trimoxazole	0	0	0	0	0	0	1	12.5	0	0	0	0	1	2
Cefotaxime	3	27.3	0	0	7	28	1	12.5	0	0	0	0	11	21.6
Not sure of which to select	4	36.4	3	100	6	24	5	62.5	0	0	1	50	19	37.3
Total	11	100	3	100	25	100	8	100	2	100	2	50	51	100

Table 4.3.40: Frequency distribution of respondents according to their indications of antibiotics of choice in gram-negative bacilli infections of surgical wound. (Question 19)

Antibiotic selection options	Frequencies of respondents by qualifications and according to indications of antibiotics of choice													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
Ampicillin	1	9.1	0	0	2	8	2	25	1	50	1	50	7	13.7
Co-trimoxazole	0	0	0	0	2	8	0	0	0	0	0	0	2	3.9
Cefotaxime	7	63.6	1	33.3	12	48	2	25	0	0	0	0	22	43.1
Not sure of which to select	3	27.3	2	66.7	9	36	4	50	1	50	1	50	20	39.2
Total	11	100	3	100	25	100	8	100	2	100	2	100	51	100

- 3.9% (n = 2) incorrectly selected co-trimoxazole rather than cefotaxime and presumably lack knowledge of the activity of co-trimoxazole against *Pseudomonas*;
- 13.7% (n = 7) selected ampicillin rather than cefotaxime and co-trimoxazole and thus demonstrated their lack of knowledge of the low activity of the ampicillin in comparison with cefotaxime and co-trimoxazole against gram-negative bacilli including *Pseudomonas*; and
- 39.2% (n = 20) admitted not being sure of which of the three antibiotics, ampicillin, co-trimoxazole and cefotaxime to use in treating gram-negative bacilli infections of surgical wounds.

◆ **Determining the extent to which cost of antibiotics and patterns of bacterial pathogen antibiotic sensitivities influence respondents' selection of antibiotics in specified clinical scenarios. (Question 20)**

Tables 4.3.41 and 4.3.42 show percentage frequency distributions of respondents according to their indications of the extent to which they consider factors of antibiotic cost and sensitivities of bacterial pathogens to antibiotics when they select antibiotics for prescription in given infections. These are summarised as outlined below.

- **The extent to which factors of cost of antibiotics influence respondents' selection of antibiotics for prescription**

Of the total number of respondents,

- 17.6% (n = 9) and 35.3% (n =18) respectively never considered cost as a factor or considered it only to a minor extent when they selected antibiotics for prescribing in treating infections. This accounted for a total of 52.9% of respondents indicating they never or only to minor degrees considered costs of antibiotics when they decided which antibiotics to prescribe in given infections;
- 35.3% (n = 18) considered the factor of cost of antibiotics when they selected which antibiotic to prescribe; and
- 9.8% (n = 5) respondents did not indicate the extent to which they considered the factor of cost when they selected antibiotics for prescription.

- **The extent to which bacterial pathogen antibiotic sensitivity as a factor influences respondents' selection of antibiotics for prescription**

° A majority of 76.5% (n = 39) respondents in total reported considering the factor to major degrees as they decided on which antibiotics to select from a group of available antibiotics in treating bacterial infections.

° Respondents not considering the factor of bacterial pathogen antibiotic sensitivity at all or considering it to a minor extent as they decided on which antibiotics to select for prescribing represented only 13.7% (n= 7) of a total number of respondents. .

- **Other factors indicated by respondents as influencing their selection of antibiotics in treating infections in practice**

Other factors indicated by respondents as influencing their decisions to select antibiotics for prescription are shown in Table 4.3.43 and outlined as indicated below.

° In total 29.4% (n = 15) of respondents indicated other factors other than those of cost and pathogen antibiotic sensitivity as factors they considered as they selected antibiotics for prescription and included one drug- and five patient-related factors.

° **Drug-related factors**: Of the total number of respondents and as factors they considered as they prescribed antibiotics, two **(3.9%)** indicated *drug dosage regimen of available antibiotics.*

° **Patient-related factors**: Of the total number respondents and also as factors *they considered as they prescribed antibiotics,*

– 5.9% (n= 3) made up of 12% (3 out of 25) of general practitioners indicated *patient sensitivity to antibiotics*;

– 7.8% (n = 4) composed respectively of 18.2% (2 out of 11) and 8% (2 out of 25) of physician specialists and general practitioners indicated *severity of illness*;

– 3.9% (n = 2) comprising 9.1% of physician specialists (1 out of 11) and 4% (1 out of 25) of general practitioners cited *site of infection*;

Table 4.3.41 Frequency distributions of respondents according to degrees to which they consider in practice factors of cost of antibiotics in the selection of antibiotics.

Degrees of antibiotic cost factor consideration	Frequencies of respondents by qualifications and according to indications of degrees of antibiotic cost factor consideration.													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
Not at all	2	18.2	0.0	0	3	12.0	2	25.0	1	50	1	50	9	17.6
Minor degree	7	63.6	0.0	0	9	36.0	2	25.0	0	0.0	0	0.0	18	35.3
Subtotal (Not at all and minor degree)	9	81.8	0.0	0	12	48	4	50	1	50	1	50	27	52.9
Major degree	1	9.1	2.0	66.7	13	52.0	2	25.0	0	0.0	0	0.0	18	35.3
No response	1	9.1	1.0	33.3	0	0.0	2	25.0	1	50	1	50	6	11.8
Total	**11**	**100**	**3.0**	**100**	**25**	**100**	**8**	**100**	**2**	**100**	**2**	**100**	**51**	**100**

Table 4.3.42 Frequency distributions of respondents according to degrees to which they consider in practice factors of bacterial pathogen antibiotic sensitivity in the selection of antibiotics.

Degrees of antibiotic cost factor consideration	Frequencies respondents by qualifications and according to indications of degrees of antibiotic cost factor consideration.													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
Not at all	0	0.0	0	0.0	1	4.0	0	0.0	0	0.0	0	0.0	1	2
Minor degree	1	9.1	0	0.0	4	16.0	1	12.5	0	0.0	0	0.0	6	11.8
Subtotal (Not at all and minor degree)	1	9.1	0	0.0	5	20.0	1	12.5	0	0.0	0	0.0	7	13.7
Major degree	10	90.9	2	66.7	19	76.0	5	62.5	2	100	1	50.0	39	76.5
No response	0	0.0	1	33.3	1	4.0	2	25.0	0	0.0	1	50.0	5	9.8
Total	**11**	**100**	**3**	**100**	**25**	**100**	**8**	**100**	**2**	**100**	**2**	**100**	**51**	**100**

Table 4.3.43 Frequency distributions of respondents according to other factors considered in the selection of antibiotics.

Other factors consideration	Frequencies of respondents by qualifications and according to other factors considered in the selection of antibiotics													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
Regimen of antibiotic administration	0	0	0	0	1	4	1	12.5	0	0	0	0	2	3.9
Brand of antibiotic: credibility of antibiotic manufacturer	0	0	0	0	1	4	0	0	0	0	0	0	1	2
Patient sensitivity to antibiotic	0	0	0	0	3	12	0	0	0	0	0	0	3	5.9
Severity of illness/ Patients general condition	2	18.2	0	0	2	8	0	0	0	0	0	0	4	7.8
Site of infection	1	9.1	0	0	1	4	0	0	0	0	0	0	2	3.9
Past medical history /Recurrence of infection	1	9.1	0	0	0	0	0	0	0	0	1	50	2	3.9
Consequences of not treating Adequately	1	9.1	0	0	0	0	0	0	0	0	0	0	1	2
Sub total	**5**	**45.5**	**0**	**0**	**8**	**32**	**1**	**12.5**	**0**	**0**	**1**	**50**	**15**	**29.4**
No factor indicated	6	54.5	3	100	17	68	7	87.5	2	100	1	50	36	70.6
Total	**11**	**100**	**3**	**100**	**25**	**100**	**8**	**100**	**2**	**100**	**2**	**100**	**51**	**100**

- 3.9% (n = 2) made up of 9.1% (1 out 11) of physician specialists and 50% (1out of 2) of nursing assistants cited *patient's past medical history or recurrence of infection*; and
- 2% made up of 9.1% (1 out of 11) physician specialists who said they considered consequences of not treating the patients.

4.3.5.2 Results Evaluations and Discussion

- **Analysis of respondents' score data**

The importance of good knowledge display as a factor in the appropriate prescribing and use of antibiotics is implied in a statement by Chambers (2001:1146) when he indicated in a chapter he wrote on antimicrobial agents in Goodman and Gillmans' the Pharmacological basis of Therapeutics. He emphasised that optimal and judicious selection of antimicrobial agents for therapy of infectious diseases requires clinical judgement and detailed knowledge of pharmacological and microbial factors. In their article on antibiotic prescribing and lessons thereof for physicians, Nathwani and Davey (1999:288) documented reasons for inappropriate prescribing, among others, as insufficient training in infectious diseases and antibiotic treatment and also insufficient use of antimicrobial information. By interpretation, the authors' reasons attribute causes of inappropriate antibiotic prescribing to prescribers' insufficient knowledge of infectious diseases and antibiotic treatment or the insufficient utilisation of such knowledge. On the basis of the indications of these authors of the importance of the prescriber's knowledge in determining the appropriateness of antibiotic prescriptions, one ordinarily would expect positive correlations between levels of knowledge prescribers have with respect to the bacteriology of infections and principles of appropriate antibiotic prescribing as this study investigated as well as the extent to which antibiotics are appropriately prescribed.

According to further notations in this chapter, Chambers (2001:1146) indicated that a prescriber's decision on the use of antibiotics, rather unfortunately, is frequently made lightly without regard to the potential infecting microorganism or to the pharmacological features of the drug. This important notation tends to imply that prescribers of antibiotics do often prescribe the drugs without due consideration of the presence or the characteristics of the infecting bacterial pathogens. It causes doubts as to whether

indeed prescribers' level of knowledge in bacteriology and principles of antibiotic prescribing or the extent to which prescribers apply such knowledge to determine the appropriateness of antibiotic prescriptions. Cadieux *et al.* (2007:881) studied the effect of knowledge on appropriateness of antibiotic prescribers using scores of licensure examinations which among other things tested candidates' knowledge of infectious diseases and antibiotics. The results of their study found no association between scores on licensure examinations and inappropriate antibiotic prescribing. Among other reasons that they gave as possible explanation for this, was their speculation that knowledge may not be the most important determinant of inappropriate antibiotic prescribing.

- **Lack of knowledge in bacteriology and principles of antibiotic prescribing: Does it exist among prescribes?**

Questions used in testing the level of prescribers' knowledge in this study were designed with the purpose of testing what was considered basic for prescribers' to know about the characteristics of both infecting bacterial pathogens and antimicrobial agents that could possibly be used in their successful treatment and their ability to select correctly from a list of given antibiotics the most appropriate antibacterial agent for treating the infection.
It is presumed on the basis of the type of questions asked that respondents' level of performance in the test will directly reflect the extent of their knowledge in antibiotic prescribing and hence their ability to select antibiotics appropriately for prescribing.
As results indicate 41.2% of respondents in total and who are composed mainly of physician specialist and general practitioner qualifications, scored marks in the performance level range that descriptively graded respondents as having "fair to very good knowledge" in bacteriology of infections and principles of antibiotic prescribing (Table 4.3.26). A corresponding 58.8% of respondents of all qualifications had scores in the range that also graded respondents as having "poor to very poor knowledge" in the indicated subject area of the test. The shape of the histogram of respondents' scores by definitions of Utts and Heckard (2007:33) is seen to be skew to the right and showed fewer respondents with higher scores and indicating higher numbers of respondents with lower scores and hence poorer knowledge in principles of antibiotic selection and prescribing within the population of respondents than those with higher scores and better knowledge.

By these results lack of adequate knowledge in bacteriology and principles of appropriate prescribing among respondents has been established and is considered as a factor that may contribute to improper antibiotic prescribing within study sites.

The impact of prescriber knowledge in bacteriology of infections and principles of appropriate prescribing of antibiotics on the appropriateness of antibiotic prescriptions

Results of both antibiotic prescription analysis data as shown in Section 4.1.1 and respondents' knowledge test as contained in survey data have been jointly analysed to determine prescribers' knowledge in bacteriology of infections and principles of antibiotic prescribing and whether their level of knowledge would influence their ability to prescribe antibiotics appropriately. The determination assumed a close correlation between the two sets of data on the basis of the following:

- Procedure of prescription assessment was based on the extent to which prescribers adhere to principles of antibiotic prescribing.
- The survey was conducted among prescribers responsible for writing antibiotic prescriptions and data were analysed.
- Results of analysis of the survey data showed that the majority of doctor respondents and all doctor respondents plus a few nurse clinician respondents respectively consulted and treated patients at study site inpatient and outpatient departments where prescription data were collected and analysed for their appropriateness.
- The survey targeted all prescribers at study site hospitals and associated with health service areas. Though all prescriber respondents could not be reached, the majority were and the response rate was high (Table 4.3.1). This implies that with the exception of a few prescribers who did not take part in the survey, the majority who took part were indeed responsible for antibiotic prescriptions the data were analysed.

Manners in which assessed prescriptions were written, until disproved otherwise, were further assumed to partly reflect the knowledge of prescribers in bacteriology of infections and principles of antibiotic prescribing. The tenet of the analysis of the joint data was thus based on the assumption that the pattern of percentage distribution of

respondents according to their performance in the knowledge test would be similar to the pattern of distribution of appropriately and inappropriately prescribed antibiotics.

Descriptive evaluation of results of joint knowledge test and prescription analysis data

The percentage of respondents with "fair to very good knowledge" prescribing antibiotics in inpatient departments is estimated as 63.6% (21 out of 33 doctor respondents who see and treat inpatients) (Table 4.3.26). If it is assumed that respondents with "fair to very good knowledge" in bacteriology of infections and principles of antibiotic prescribing would prescribe antibiotics appropriately on account of their knowledge in the treatment of infectious diseases, then chances are that an estimated 63.6% of inpatient antibiotic prescriptions assessed would be appropriately prescribed in proportion to the 63.6% of respondents with "fair to very good knowledge".

Doctor and nurse clinician respondents who see and treat patients at study site outpatient departments from which prescriptions were collected for assessment totalled 40 (determined from Table 4.3.4.). This number of respondents can be said to form the majority group of prescribers responsible for outpatient prescriptions analysed for their appropriateness. With the number of respondents obtaining test score marks in the range describing them as having "fair to very good knowledge" in bacteriology of infections and principles of antibiotic prescribing being 21, a 52.5% (21 out of 40) of respondents with such "fair to very good knowledge" can be said to be responsible for prescribing outpatient prescriptions. Based on similar assumptions indicated in the case of inpatients, it is predicted that an estimated 52.5% of outpatient prescriptions assessed would be appropriately prescribed.

According to results presentations of study Phase I, appropriately written prescriptions from samples of antibiotic prescriptions analysed showed that 32.2% of inpatient (Table 4.1.1, Section 4.1.1.1) and 78.3% of outpatient (Table 4.1.24, Section 4.1.2.1) prescriptions assessed were appropriately written. By comparison the estimated 63.6% of inpatient prescriptions predicted to be appropriately written as indicated is much above the actual determined 32.2% of inpatient prescriptions found to be appropriately written as documented by the results of the prescription analysis. In contrast the estimated 52.5% of outpatient prescriptions similarly predicted to be appropriately written

is much lower than the 78.4% of this category of prescriptions found to be appropriately written.

These noted differences do not indicate a positive association between prescribers' knowledge either in bacteriology of infections or principles of appropriate antibiotic prescribing and their ability to appropriately prescribe antibiotics by this study. A number of reasons could be given in explanation. Notably, however, limitations of the procedure used in determining antibiotic prescriptions predicted to be appropriately written if prescribers' knowledge in bacteriology and principles of antibiotic prescribing were a determinant of appropriateness of antibiotic prescriptions, may be accountable. The procedure was based on assumptions, some of which perhaps may not be substantive. Some such reasons include the fact that

- not all subject matter of questions used in the knowledge test are applied for every prescription that is written. As seen with the outpatient prescriptions for example, the demands of the knowledge test may perhaps be higher than knowledge needed to write these prescriptions, and The vice versa in the case of inpatient prescriptions; and
- despite collecting both types of data from the same study sites, it may not necessarily be the same respondents who wrote all analysed prescriptions as the evaluation of the results presumed. Associations between prescribers' knowledge and appropriateness of prescribed antibiotics as determined by methods used in this study may be more substantive in the opinion of the researcher, if prescribers who prescribed analysed prescriptions were indeed the same prescribers who responded to questionnaires as the method assumed.

Albeit limitations of procedures used in determining predicted percentage proportions of appropriately written antibiotic prescriptions, results obtained confirmed findings of Cadieux *et al.* (2007:881) which reported not finding any association between prescribers' knowledge in infectious diseases and their treatment and appropriateness of antibiotic prescribing. It also gave credence to the researcher's speculation that knowledge may not be the most important determinant of inappropriate antibiotic prescribing. The significant discrepancy between expected percentage proportions of appropriately written prescription based on results of the knowledge test and actually determined proportions of such prescriptions from the sample of inpatient prescriptions

analysed, established the non-use by prescribers of their knowledge in principles of antibiotic prescribing. This also highlights Chamber's (2005:1146) reservations about the extent to which prescribers apply their knowledge when they prescribe antibiotics.

- **Comparative assessment of prescriber qualifications and their knowledge in antibiotic prescribing**

Distribution curves of respondents' test performance levels according to their qualifications showed physician specialists and general practitioners in the doctor category of respondents having higher knowledge generally in bacteriology of infections and principles of antibiotic prescribing than surgical consultants, who all were rated as having "poor to very poor" knowledge in principles of antibiotic prescribing by their performance levels (Table 4.3.26). With greater percentages of their numbers rated as having "good to very good" or their lesser percentages similarly rated as having "poor to very poor" knowledge in bacteriology and antibiotic treatment of infections than physician specialists, general practitioners can be said to exhibit more knowledge than physician specialists in bacteriology of infections and principles of antibiotic prescribing (Table 4.3.26).

Respondents of the nursing cadre generally have poor to very poor knowledge in bacteriology of infections and principles of antibiotic prescribing. In spite of this observed show of poor knowledge in the characteristics of bacterial pathogens or antimicrobial agents employed in their treatment, nurse clinicians were seen to capably prescribe antibiotics appropriately. Out of 118 prescriptions written by the qualification group and assessed for their appropriateness as reported in study Phase I, as many as 29.7% and 50.8% were appropriately written respectively according to principles of antibiotic prescribing for absolute and possible infections. On comparative basis results of study Phase I also reported doctors in the overall seen to prescribe antibiotics inappropriately more often than nurse clinicians (Table 4.1.24, Section 4.1.2.1). This interpreted from perspectives of doctors' demonstration of higher knowledge than nurse clinicians *vis a vis* indicated observed contrast between knowledge display of nurse clinicians and the extent to which they wrote antibiotic prescriptions appropriately. Further questions expected positive association of prescribers' knowledge in bacterial infections and their treatment and the appropriateness of antibiotic prescriptions as indicated in earlier paragraphs.

- **Predictions of appropriateness of antibiotic prescribing in respiratory and urinary tract infections based on prescribers' knowledge in signs and symptoms and associated bacterial pathogens of the infections**

Establishing the presence of infections through presenting signs and symptoms or other means and knowing the types and morphological characteristics of pathogens commonly associated with them are fundamental requirements for the appropriate selection and successful use of antibiotics in treating infections (Guglielmo, 2008:56-1). Antibiotic prescribing in clinical scenarios in which such fundamental principles are ignored has high chances of being done inappropriately. In antibiotic prescribing knowledge assessment tests in which questions testing prescribers' knowledge are based on infections most commonly treated by the group of prescribers being tested, chances are that results will be obtained that will depict the impact of prescribers' display of knowledge on the appropriateness of antibiotic prescriptions they give in treating such infections. Such results can also be interpreted to indicate the extent to which prescribers' knowledge in bacterial infections serve as a factor in determining the appropriateness of antibiotic prescriptions they write.

Respiratory tract infections (RTI) and urinary tract infections (UTI) are the first and second most prevalent infections prescribers treat in outpatient departments in Lesotho (Ministry of Health & Social Welfare. 2002:161p) and obviously the category of infections for which antibiotics are most often prescribed. For purposes of determining the extent to which prescribers' display of knowledge has an impact on their antibiotic prescribing in practice or serve as a factor determining degrees to which antibiotics are prescribed appropriately or inappropriately in out patient departments, the two types of infections have been selected for this aspect of the study.

- **Predictions of appropriateness of antibiotic prescribing in upper respiratory tract infections**

A test of knowledge of respondents' identification of signs and symptoms of bacterial infections of the upper respiratory tract (URT) showed a majority (78.4%) as against 21.6% of total respondents displaying inadequate knowledge in their recognition of signs and symptoms deemed necessary to be present to warrant antibiotic prescribing in cases presenting as infections of the URT (Table 4.3.27). The indicated percentage of respondents either mentioned signs and symptoms not indicative of or not absolute for

bacterial infections of the URT or failed to indicate any signs and symptoms demonstrative of bacterial infections of the tract (Table 4.3.28). This detection of inadequate knowledge was seen to be demonstrated by all qualifications groupsof respondents including physician specialists and general practitioners, 81.8% and 64.0% of whom were respectively seen failing to indicate signs and symptoms suggestive of bacterial infections of the URT.

By interpretation, the 78.4% of respondents seen to lack knowledge in signs and symptoms recognised as establishing bacterial infections of the URT would prescribe antibiotics injudiciously for such cases on account of their inability to differentiate bacterial from non-bacterial infections of the tract. According to interpretations given to Utts and Heckard's (2007:234) definition of relative frequency probabilities, the proportion of individuals who have a given characteristic among a given group of individuals can be taken as the probability of an individual having that characteristic among the given group of individuals. Applied in the context of evaluations of these results, the probability of a prescriber among the group of prescribers lacking knowledge in signs and symptoms of URTI is equivalent to the proportion of individuals lacking this knowledge among the group. This is equal to 0.78. The extent to which a given prescription is appropriately written by logical reasoning is determined by the characteristic or the antibiotic prescribing behaviour of the prescriber writing such a prescription. Based on this, it is deduced that the percentage proportion of antibiotic prescriptions written inappropriately on account of prescribers' lack of knowledge in signs and symptoms of bacterial infections of the URT will be equivalent to the 78.4% proportion of prescribers lacking this knowledge. The probability of a prescription being written inappropriately on account of prescribed antibiotics being indicated for clinical conditions for which bacterial infections have not been established due to prescribers' lack of knowledge on the subject will be equivalent to the indicated 78.4% proportion of such prescriptions among the total number of prescriptions written by all respondents. This again is 0.78 in accordance with Utts and Heckard's (2007:234) definition of relative frequency probabilities. By similar reasoning, the probability of antibiotic prescriptions being written appropriately for URTI is determined as 0.22, the equivalence of the 21.6% proportion of respondents with the requisite knowledge of signs and symptoms of infections of the URT.

Compared to their knowledge level in the recognition of signs and symptoms of bacterial infections of URTI, respondents generally can be said to demonstrate fairly good knowledge in bacteriology of URTI. Approximately half of their total number [49.0% (n = 25) as against 51.0% (n = 26)] correctly indicated bacterial pathogens commonly associated with URTI (Table 4.3.34). Using these percentage proportions of respondents correctly and incorrectly indicating bacterial pathogens associated with infections of the URT, the probabilities of prescriptions being written appropriately and inappropriately by respondents for URTI if prescriptions are assessed based on prescribers' ability to prescribe antibiotics targeting associated pathogens of the URT are determined as 0.49 and 0.51.

In the event of prescriptions written by all 51 respondents being assessed for their appropriateness on the basis of whether or not antibiotics were prescribed for established cases of bacterial infections of the URT and to target bacterial pathogens associated with URTI, prescriptions that will be adjudged appropriately and inappropriately written will have probabilities of 0.11 (0.22 multiplied by 0.49) and 0.40 (0.78 multiplied by 0.51) of being written. According to Utts and Heckard (2007:246) the probability of two independent events occurring simultaneously is the product of the probabilities of the two independent events. Writing an antibiotic prescription appropriately for an established infection and selecting prescribed antibiotic(s) to target given pathogen(s) are two independent events which need to occur together for a prescription in the scenario given above to be seen as being appropriately written. The probabilities of these two independent events are respectively 0.22 and 0.49.

The higher probability of 0.40 of antibiotic prescriptions being written inappropriately for URTI as compared to the much lower 0.11 of their being written appropriately for the infections by interpretation, indicates that respondents have higher tendencies of writing antibiotic prescriptions inappropriately for URTI in practice. This is attributable more to respondents' lack of knowledge in signs and symptoms of bacterial infections of the URT than to their lack of knowledge in bacterial pathogens associated with the infection. Evidence of this is shown by the higher 0.78 probability of prescriptions being written inappropriately based on respondents' inability to establish presence of bacterial infections by signs and symptoms than the lower 0.51 probability of prescriptions being

written inappropriately for the infections due to prescribers' inability to select antibiotics appropriately to target infecting pathogens.

The estimated high probabilities of 0.78 and 0.51 of prescriptions being written inappropriately as consequence of respondents' respective show of inadequate knowledge of signs and symptoms establishing bacteria infections of the URT and of target pathogens commonly responsible for infections of the tract can again be interpreted to indicate a negative impact of prescribers' lack of knowledge in aspects of the investigated characteristics of URTI on appropriateness of antibiotic prescriptions for the infection. It also suggests a positive association between prescribers' knowledge in the characteristics of the infection as investigated and their ability to prescribe antibiotics appropriately. These said though, it is remarked that the inferences are not made from findings from comparisons of these results with results from analysis of any practical data as was done in the analysis of respondents' score data which showed no associations between prescribers' knowledge levels in infections and appropriateness of prescribed antibiotics. The existence of a positive association between prescribers' knowledge in the characteristics of URTIs and their ability to prescribe antibiotics appropriately as results of this analysis purports, underscores prescribers' lack of knowledge on the characteristics of URTIs as one major reason for inappropriate prescribing of antibiotics for the infections. Acknowledging inappropriate prescribing of antibiotics for URTIs, Gonzales *et al.* (2001:690) noted that the majority of antibiotics prescribed for adults in ambulatory practice in the United States are for sinusitis, acute pharyngitis, acute bronchitis and non-specific URTIs including the common cold. According to the authors, routine antibiotic treatment for each of these conditions, particularly colds, non-specific URTIs and acute bronchitis is not needed. Large proportions of antibiotics prescribed for these conditions further to the authors' notations, are unlikely to provide clinical benefits to patients.

- **Predictions of appropriateness of antibiotic prescribing in lower respiratory tract infections (LRTI)**

An overall 60.8% of respondents correctly indicated signs and symptoms considered indicative of bacterial infections of the lower respiratory tract (LRT). This is against a much lower 39.2% of respondents who gave no indications of such signs and symptoms or indicated signs and symptoms which were neither not indicative nor absolute for

bacterial infections of the LRT (Tables 4.3.29 and 4.3 30). This subgroup of respondents are considered having insufficient knowledge in signs and symptoms of LRTI and are incapable of establishing presence of bacterial infections of the LRT to justify their prescription of antibiotics. The indicated 60.8% of respondents who correctly indicated signs and symptoms of lower respiratory tract infections (LRTI) in the alternative are considered having the knowledge needed to establish bacterial infections of the LRT to warrant the prescription of antibiotics.

In respect of respondents' knowledge display in the bacteriology of LRTI, a little over half the total number of respondents [51%] were seen to demonstrate good knowledge in bacteriology of LRTI by correctly indicating bacterial pathogens known to be associated with the infections. This is against 49.0% who indicated no such bacterial pathogens and are considered having inadequate knowledge in bacterial pathogens associated with LRTI (Table 4.3.35 and 4.3.36).

Using the same principles and laws of probability applied in derivations establishing percentage proportions of prescriptions expected to be written appropriately or inappropriately and hence the probabilities of such prescriptions being written by respondents for URTIs, it can be shown that for LRTI,

- 60.8% and 39.2% of total prescriptions written by respondents would respectively be appropriately and inappropriately written if prescriptions were assessed using a criterion seeking to establish whether or not antibiotics were prescribed for established bacterial infections of the LRT on the basis of presenting signs and symptoms;
- the probabilities of prescriptions being written appropriately or inappropriately based on prescribers' knowledge in signs and symptoms of LRTI and application of same in establishing presence of bacterial infections before prescribing antibiotics are 0.61 and 0.39;
- 51.0% and 49.0% of prescriptions written by respondents would respectively be appropriately and inappropriately written if prescriptions are assessed using criterion seeking to establish whether or not antibiotics were prescribed to target bacteria pathogens associated with LRTI;
- the probabilities of prescriptions being written appropriately or inappropriately based on prescribers' knowledge of bacterial pathogens associated with LRTI and the

application of same in the selection of antibiotics that appropriately target pathogens associated with LRTI are respectively 0.51 and 0.49;

- the probabilities of prescriptions being written appropriately or inappropriately for LRTI based on concurrent events of prescribers' applications of their knowledge of signs and symptoms in establishing presence of bacterial infections of the tract and of bacterial pathogens associated with the tract in the selection of antibiotics that appropriately target associated pathogens of the LRT are 0.31 (0.61 multiplied by 0.51) and 0.19 (0.39 multiplied by 0.49).

Contrary to observed patterns of appropriateness of antibiotic prescribing in URTI, respondents have shown according to their knowledge levels in the characteristics of the infections investigated, higher tendencies of prescribing antibiotics appropriately than inappropriately in LRTI. This is evidenced by the higher probability of 0.31 of antibiotics being prescribed appropriately in comparison to the lower probability of 0.19 they are seen to be prescribed inappropriately. The higher probability of 0.31 of antibiotics being prescribed appropriately for LRTI in comparison with the probability of the prescription of the drugs for URTIs (0.11) or the lower probability of 0.19 of prescribing the drugs inappropriately for LRTI as compared with the 0.40 probability of the inappropriate prescribing of the drugs for URTIs also indicates respondents' display of better knowledge in their recognition of signs and symptoms and of bacterial pathogens associated with infections of the lower than the upper respiratory tract. The observation further demonstrates an existence of positive associations between prescribers' knowledge in the characteristics of infections and their ability to prescribe antibiotics appropriately.

The 0.31 probability of prescribing antibiotics appropriately based on prescribers' knowledge of the investigated characteristics of infections of the LRT, though much higher than the determined probability of 0.11 of prescribing the drugs for URTIs, is still considered low. By interpretation, this means a quite high percentage of antibiotics would be inappropriately prescribed in the treatment of LRTI as would be the case for URTIs, if decisions on antibiotic treatment and antibiotic choices are left with prescribers entirely to make. This documents a negative impact of prescribers' lack of adequate knowledge in the characteristics of respiratory tract infections (RTI) as investigated, on the appropriateness of antibiotic prescribing in respiratory tract infections, LRTI and

URTI inclusive. This show of lack of adequate knowledge in the investigated characteristics of RTI with its negative impact on antibiotic prescribing as being reported, is demonstrated by all qualification groups of respondents identified as major prescribers of antibiotics in Lesotho. Outlined in confirmation of this, results as presented above show that 63.6% (7 out of 11) and 45.5% (5 out 11) of physician specialists, 100% (3 out of 3) of surgical consultants in each case, 20.0% (5 out of 20) and 32.0% (8 out 25) of general practitioners, and 75% (6 out of 8) of nurse clinicians whom the study identified as major prescribers of antibiotics within study sites demonstrated lack of knowledge in identifying signs and symptoms and bacterial pathogens associated with LRTI (Table 4.3.2 and 4.3.36). Whether in practice such a negative impact translates into high rates of inappropriate prescribing of antibiotics for respiratory tract infections at study sites will need further investigation. According to Cadieux *et al.* (2007:881) as already reported, prescribers' knowledge levels may not be an important factor in determining the appropriateness of antibiotic prescriptions. There is need to conduct further studies that will compare appropriateness of prescribed antibiotics for URTIs and LRTI in practice with appropriateness of same prescriptions as predicted by results of this study to be able to establish the extent to which prescribers' lack of knowledge in the investigated characteristics have a negative impact on appropriateness of antibiotic prescribing for respiratory tract infections. This is particularly necessary for reasons that the referenced report by Cardieux *et al.* (2007:881) was given credence by result evaluations of respondents' score data which, as again reported, found no associations between prescribers' knowledge levels and appropriateness of antibiotic prescriptions assessed in study Phase I.

- **Predictions of appropriateness of antibiotic prescribing in non-sexually transmitted urinary tract infections (NSTUTI)**

Two thirds [66.7% (n = 34)] of respondents were seen to correctly mention signs and symptoms deemed indicative of non-sexually transmitted urinary tract infections (NSTUTI) and are considered having the knowledge level required to correctly diagnose the infection on the basis of presenting signs and symptoms. One third [33.3% (n =17)] of respondents on the other hand, gave no indications of such signs and symptoms or indicated signs and symptoms which were neither not indicative nor absolute for bacterial infections of the NSTUTI and are considered lacking required knowledge in

symptomatic diagnosis of the infection for its appropriate treatment (Tables 4.3.31 and 4.3 32).

Test of prescribers' knowledge in bacterial pathogens commonly associated with NSTUTI showed 41.2% (n = 21) of respondents ably indicating pathogens commonly associated with the infections and thus showing that they have adequate knowledge to target these pathogens as they prescribe antibiotics in treatment of the infections. The rest(58.8%) (n = 30) of respondents indicated no pathogens or indicated pathogens not associated with the infection and accordingly demonstrated their lack of knowledge of pathogens that would need to be targeted as antibiotics are prescribed in treating the infections (Tables 4.3.37 and 4.3.38).

Predictions of appropriateness of prescribed antibiotics in treating NSTUTI as determined from principles and laws of probability as applied in URTI shows percentage proportions of prescriptions expected to be written appropriately or inappropriately and the probabilities of such prescriptions being written by respondents for NSTUTI as being;

- 66.7% and 33.3% of the total number of prescriptions written by respondents would respectively be appropriately and inappropriately written if prescription assessments are based on presenting signs and symptoms as criterion used in establishing presence of bacterial infections of the urinary tract (UT);
- the probabilities of prescriptions being written appropriately or inappropriately based on prescribers' knowledge in signs and symptoms of NSTUTI and application of same in establishing presence of bacterial infections before prescribing antibiotics are 0.67 and 0.33;
- 41.2% and 58.8% of prescriptions written by respondents would respectively be appropriately and inappropriately written if prescription assessments were based on criterion seeking to establish whether or not antibiotics were prescribed to target bacterial pathogens associated with NSTUTI;
- the probabilities of prescriptions being written appropriately or inappropriately based on prescribers' knowledge of bacterial pathogens associated with NSTUTI and the application of same in the selection of antibiotics that appropriately target pathogens associated with NSTUTI are respectively 0.41 and 0.59; and
- the probabilities of prescriptions being written appropriately or inappropriately for NSTUTI based on concurrent events of prescribers' applications of their knowledge

of signs and symptoms in establishing the presence of bacterial infections of the urinary tract and of bacterial pathogens associated with the tract in the selection of antibiotics that appropriately target associated pathogens of the NSTUTI are 0.27 (0.67 multiplied by 0.41) and 0.19 (0.59 multiplied by 0.33).

Similar to patterns of appropriateness of antibiotic prescribing in LRTI, respondents show higher tendencies of prescribing antibiotics appropriately than inappropriately in NSTUTI, if appropriateness assessment of prescriptions is based on the extent to which they apply their knowledge in prescribing the drugs. This is testified to by the higher probability of 0.27 of antibiotics being prescribed appropriately in comparison to the lower probability of 0.19 of their prescribing for the infections. As similarly observed for LRTI again, the probability of 0.27 of prescribing antibiotics appropriately based on prescribers' knowledge of investigated characteristics of infections of the urinary tract, is considered low and indicative of a high percentage of antibiotics being inappropriately prescribed in the treatment of NSTUTI if decisions on antibiotic treatment of the infection are left with prescribers to make. A negative impact of prescribers' lack of adequate knowledge in the characteristics of NSTUTI as investigated on appropriateness of antibiotic prescriptions is stipulated here again as was speculated for LRTI and URTI. As in the cases of RTI, the show of lack of knowledge in signs and symptoms of NSTUTI and of bacterial pathogens associated with infections here again is demonstrated by all qualification groups of respondents identified as major prescribers of antibiotics. High percentage proportions of all qualification groups inclusive of 45.5% (5 out of 11) and 54.5% (6 out of 11) of physician specialists, 100% (3 out of 3) and 66.7% (2 out of 3) of surgical consultants, 24.0% (6 out of 25) and 40% (10 out of 25) of general practitioners and 25.0% (2 out of 8) and 100% (8 out of 8) of nurse clinicians as testified by results demonstrated inadequate knowledge in their recognition of signs and symptoms of bacterial pathogens associated with NSTUTI (Tables 4.3.32 and 4.3.38).

- **Comparative assessment of knowledge level displayed by qualification groups of respondents in antibiotic prescribing in RTI and UTI**

General practitioners in all three cases of upper and lower respiratory and urinary tract infections displayed the best knowledge in the recognition of signs and symptoms that absolutely indicate bacterial aetiologies of these three infections and the types of bacterial pathogens associated with them. This is contrary to the researcher's

expectations of physician specialists on the basis of their higher qualifications and experience, being the respondent qualification group that would show better knowledge. The better display of knowledge by general practitioners as compared to their senior counterparts cannot be explained within provisions of results of this study. It can only be speculated that infectious diseases most probably may not be the areas of specialisation of most physician specialists who participated in the study. As a point of concern, the finding is seen as raising a curtain on the problem of antibiotic management of patients by junior medical staff who, as the results suggest, seem to lack constructive supervision and guidance they may need from their senior counterparts as they treat infections.

Surgical consultants displayed the least knowledge in their recognition of signs and symptoms and of bacterial pathogens associated with respiratory and urinary tract infections. This could be expected by reasons of the specialisation and patient management responsibilities of this qualification group of respondents. Respiratory and urinary tract infections are medical problems that are not ordinarily attended to by surgeons.

Reservations of the involvement of registered nurses and nurse assistants have been expressed in discussion of results of data analysis presented in Section 4.3.1.2. The low levels of display of knowledge shown by these qualification groups of respondents underscored these reservations further by establishing without doubt that prescribers in the category of the nursing cadre, nurse clinicians inclusive, do not have the knowledge and expertise required for the appropriate prescribing of antibiotics. Nurse clinicians, unlike registered nurses and nurse assistants were identified as major prescribers of antibiotics in outpatient departments and their lack of knowledge in expertly doing this, orchestrates a stage for antibiotic misuse with its associated problems of treatment failures and promotion of antibiotic resistance development by bacterial pathogens.

- **The extent to which factors of prescribers' knowledge of morphological characteristics and antibiotic sensitivity patterns of pathogens and costs of antibiotics determine prescribers' selection of antibiotics in practice.**

Prescribers' ability to select from a group of antibiotics the most appropriate such agent in the treatment of an infection is an important factor determining how appropriately antibiotics are prescribed empirically. For a demonstration of such ability the prescriber

must be able to make sound clinical judgement of the prevailing clinical condition for which the antibiotic is required and also exhibit good knowledge in the pharmacological and antimicrobial properties of the antibiotics from which the antibiotic of choice selection is to be made (Chambers, 2005:1146). Lack of such knowledge on the part of a prescriber is indicative of a lack of basis for comparing one antibiotic with another and an inability to select from among others an antibiotic most appropriate in treating a given infection.

- **Question design and theoretical basis of their use in assessing respondents' abilities in antibiotic selection**

Questions designed to test respondents' display of their ability to select antibiotics on the basis of their pharmacological and antimicrobial properties, take into account what they necessarily need to consider in practice as they decide which antibiotic should in principle be selected rather than others as they prescribe these drugs in the treatment of infections.

In this study respondents were specifically requested to select one of three antibiotics, namely, ampicillin, co-trimoxazole and cefotaxime. The three antibiotics are among the most commonly prescribed antibiotics at study sites and respondents ordinarily are expected to know their pharmacological and antimicrobial properties that enable their appropriate selection in the treatment of given infections. To test whether respondents indeed have knowledge of these required characteristics of the antibiotics, questions asked required them to select any one of the three antibiotics that most appropriately would treat described infections, having been given the morphological descriptions of the implicating pathogens in the specified infections. Essentially questions tested respondents' ability to select any of the three antibiotics based on their knowledge of the antimicrobial activities of the listed antibiotics and the types of bacterial pathogens that are to be targeted against having been provided information on the morphological descriptions of the infecting pathogens. Inclusive of what respondents are to know as a demonstration of their knowledge and ability to select antibiotics appropriately are outlined as follows:

– Where cocci are microscopically identified as infecting organisms of a surgical wound, the most likely pathogens to be involved as far as the site of infection is concerned should be staphylococci (*Staphylococcus aureus* and *Staphylococcus epidermidis*) while not ruling out streptococci particularly *enterococci, the* non-

haemolytic streptococci which are known to produce infections in patients in whom mucosal or epithelial cells have been disrupted (Lowy, 2005:817; Wessels, 2005:830).

- Where gram-negative bacilli are the microscopically identified organisms, *Escherichia coli, Klebsiella spp, Proteus spp* and *Pseudomonas spp,* should be the pathogens of suspect (Russo, 2005: 881, 882 & 883; Ohl & Pollack, 2005:892).
- Sensitivity patterns of these organisms to the listed antibiotics.
- Where staphylococci infections are concerned there is the possibility of such organisms being methicillin resistant strains.
- Co-trimoxazole and not ampicillin or cefotaxime is an antibiotic of choice against methicillin resistant *Staphylococci aureus* and should preferably be selected rather than either ampicillin or cefotaxime in the treatment of such staphylococci infections (Guglielmo, 2008:56-9).
- Where gram-negative bacilli are microscopically identified as suspect pathogens in an infection, the possibility of *Pseudomonas* and *Klebsiella* spp being among the likely pathogens should give the urge of cefotaxime rather than ampicillin and co-trimoxazole when a choice is to be made among the three antibiotics in the treatment of such infections.
- Ampicillin has no appreciable effect against *Pseudomonas* and *Klebsiella* spp while co-trimoxazole show activity against *Klebsiella* spp but not *Pseudomonas* (Guglielmo, 2008:56-10).
- Cefotaxime among the three antibiotics shows appreciable activity against all four gram-negative bacilli and should be the antibiotic of choice for empirical prescription for the described clinical scenario in absence of culture sensitivity test results (Guglielmo, 2008:56-9, 56-10).

A correct selection of any of the three listed antibiotics rather than the other two as the antibiotic of choice in the treatment of the described infections indicates respondents' practical display of knowledge in the selection and appropriate prescription of these antibiotics.

- **Assessment of respondents' ability to make antibiotic choices based on their knowledge of antimicrobial characteristics of antibiotics**

Two per cent of the total number of respondents comprised of one nurse clinician selected co-trimoxazole rather than ampicillin and cefotaxime as antibiotic of choice in

treating hypothesised gram-positive infections of surgical wounds as the question stipulated (Table 4.3.39). This implies that all respondents with the exception of the one nurse clinician who selected co-trimoxazole rather than ampicillin and cefotaxime, either overlooked the possibility of methicillin resistant staphylococci being implicated in the infection or did not know the antimicrobial properties of indicated antibiotics well enough. A prescriber with a good enough knowledge on the characteristics of staphylococci, would be able to select co-trimoxazole instead of ampicillin or cefotaxime on basis of the former antibiotic having activity against methicillin resistant strains of *Staphylococcus aureus* while the latter two do not. In an alternative assessment that further demonstrated respondents' lack of knowledge in the antimicrobial properties of the listed three antibiotics from which a selection was to be made, 39.2% and 21.6% of respondents were seen to respectively select ampicillin and cefotaxime, rather than co-trimoxazole as the antibiotics of choice in treating the infection. As many as 37.3% (n=19) admitted not knowing which antibiotics to choose. Regarding respondents' ability to select the most appropriate antibiotic from the listed three antibiotics in treating gram-negative bacilli infections, less than half the total number of respondents [43.1%] selected cefotaxime over ampicillin and co-trimoxazole. The rest (56.9%) either admitted not knowing which antibiotic to choose or chose ampicillin or co-trimoxazole rather than cefotaxime in treating the hypothesised gram-negative bacilli infections. In an overall assessment, it can be said that respondents' lacked knowledge on antimicrobial characteristics of antibiotics as required for the selection of the most appropriate of the agents in treating infections. This is inferred from the high percentage of respondents observed not to have been able to select the appropriate antibiotic of choice from the listed three antibiotics in treating either of the hypothesised gram-positive cocci or gram-negative bacilli infections. It is predictive of high rates of inappropriate prescribing of antibiotics among prescribers.

The use of a clinical scenario that describes a situation in the surgical ward in the question design partly tested the expertise of surgical consultants participating in the study specifically in their display of knowledge and hence ability to select antibiotics in the treatment of surgical wound infections. The 100% (3 out of 3) of respondents in the qualification category of surgical consultants indicating not being sure of what antibiotic among the three listed antibiotics to prescribe in gram-positive cocci infections of surgical wounds or the 66.7% (2 out 3) of them failing to select cefotaxime among the

three antibiotics in treating gram-negative bacilli infections of such wounds demonstrate a significant lack of knowledge by the qualification group in antimicrobial characteristics of antibiotics.

- **The extent to which costs of antibiotics and pathogen antibiotic sensitivity patterns determines respondents' choices of antibiotics**

As many as 52.9% of respondents composed of a majority 81.8% (of physician specialists and approximately the total numbers of general practitioners and nurses) never consider cost of antibiotics as a factor or considered it only to a minor extent when they decided on which antibiotics to prescribe in the treatment of infections. A minority 35.3% only would consider the factor of antibiotic cost to a major extent when they made choices of the drugs for prescribing.

With the exception of the fluoroquinolone, ciprofloxacin, or the antibiotic/bacterial enzyme inhibitor formulation, amoxycillin/clavulanic acid which are comparatively more recent and more expensive, antibiotics used in Lesotho public health institutions are mainly the much less expensive and older often referred to "traditional antibiotics". Costs of daily treatments with these antibiotics are generally low and vary little. By estimation and using costs of antibiotics as of June 2006, these are approximated at between R0.24 to R2.80 for the oral formulations, with an outlier higher value of R11.36 for nalidixic acid. Similar estimates give costs of daily treatments of R6.40 to R22.04 for parenteral preparations with lower outlier values of R1.20 and R2.72 for gentamicin and ampicillin injections (Appendix 12: List of antibiotics commonly used at study sites with their costs as of June 2006). With little variations among costs of antibiotics which as noted, particularly for the oral formulations, are already low, cost of antibiotics as a majority of respondents indicated may indeed not be an important factor influencing respondents' decisions as they make their choices of antibiotics for prescribing. Patient factors like seriousness of infection being treated may also dictate choices of antibiotic formulations to an extent that make irrelevant cost considerations between oral and parenteral preparations.

The study did not investigate sources from which respondents obtain information from on costs of antibiotics to enable them to use this as factor in deciding what antibiotic to select from a given list of available antibiotics. What is known, however, is the fact that

essential medicines list (EML) or standard treatment guidelines (STG) that are made available to prescribers as reference booklets for their guidance in the selection of drugs they prescribe in patient management do not contain any information on costs of antibiotics or any drugs for that matter (Ministry of Health & Social Welfare, Lesotho Essential Medicines List, 2006:18-20; Ministry of Health & Social Welfare, Lesotho Standard Treatment Guidelines, 2006:1-173).

By implication, respondents ordinarily have not been seen to have any institutionalised means of knowing costs of antibiotics to enable them to make comparisons as they make their choices of antibiotics. This said though, it is possible that respondents are aware of the higher costs of the more recent antibiotics and may be more inclined to prescribing the cheaper "traditional antibiotics" if they consider costs of antibiotics as they make their choices of these drugs for prescribing. Interpreted this way, respondents indicating that they considered the factor of cost as they prescribed antibiotics may be seen to indicate their preferences for traditional antibiotics rather than more recent the newer ones on the basis of costs rather than their actual comparisons of costs of antibiotics when they make decisions on antibiotics to prescribe. On a relevant note, respondents' claims of the factor of cost featuring in their decisions of antibiotics may actually be taken as their attestations to the importance of costs as a factor in antibiotic selection. With this notation, and despite conclusions of costs of antibiotics not being an important factor influencing prescribers' choices of antibiotics, respondents are believed to willingly consider costs of antibiotics among other factors as they make their choices of which antibiotics to prescribe if they are provided with an institutionalised means of knowing and comparing costs of antibiotics.

Evidenced by the majority (76.5%) of their total number indicating that they considered antibiotic sensitivity patterns of bacterial pathogens to major extents as they make choices of antibiotics, respondents generally can be said to give considerations to exhibited patterns of sensitivities of bacterial pathogens to antibiotics as they decide on which antibiotics to prescribe in treating infections. The extent to which this influence is translated into good antibiotic prescribing by prescribers to ensure that antibiotics are appropriately selected and prescribed in the empiric treatment of infections is however doubtfully significant. High percentage proportions of all qualification groups of respondents failed to select appropriate antibiotics or admitted not knowing what

antibiotic to select in treating infections described in knowledge test questions embodied in research questionnaire. This established respondents' lack of knowledge in activity patterns of antibiotics against bacterial pathogens and suggested respondents' inability to prescribe antibiotics in line with bacterial pathogen antibiotic sensitivity patterns in the empiric treatment of infections. This notwithstanding however, the high percentage of respondents indicating that they considered patterns of bacterial pathogen sensitivities to antibiotics as they made their choices of antibiotics, is seen as generally establishing consensus among respondents that pathogen sensitivity to antibiotics is a major and an important deciding factor that determines choice of antibiotics to use in treating infections. The knowledge and information prescribers need to do this as study results confirmed is what is lacking. This suggests that if adequate information on local antibiotic sensitivity patterns of pathogens were to be disseminated to prescribers in an institutionalised information flow system originating from medical laboratories and pharmacies of hospitals, prescribers would become empowered with the knowledge and information they need to usefully consider the factor of bacterial pathogen antibiotic sensitivity in the selection of antibiotics to prescribe in the empiric treatment of infections. Contents of such proposed institutionalised information flow system on appropriate antibiotic prescribing and activities for its implementation are suggested to include the following:

- Local antibiograms, constructed by microbiology laboratories of study sites based on results of bacterial pathogen antibiotic sensitivity data analysis.
- Tables of percentage overall activities (POA) of antibiotics and antibiotic selection factors (ASF) as promulgated in study Phase II (Section 4.2.4).
- Education of prescribers on the uses of these instruments in selecting antibiotics for the empiric treatment of infections.

The development and adoption of such an information flow system by health institutions has the potential of providing a solution to the problem of inappropriate antibiotic prescribing in Lesotho public health institutions. It bridges the gap between prescribers' knowledge in antibiotic prescribing and their ability to prescribe antibiotics appropriately.

- **Prescriber indicated factors influencing choices of antibiotics**

A minority of respondents (29.4%) cited factors other than the investigated factors of cost and pathogen sensitivity to antibiotics as influencing their decisions in making antibiotic choices. These include their mention of *antibiotic dosage regimen*, a drug-

related factor, and such other factors as *brand of antibiotic or credibility of antibiotic manufacturer, sensitivity of patients to antibiotics*, *severity of illness*, *site of infection, recurrence of infections and consequences of not treating patients* all of which are patient-related. All factors as listed were indicated mainly by physician specialists and general practitioners and demonstrate basically very diverse reasons for which these qualification groups of prescribers would select or even decide to prescribe antibiotics for the treatment of infection. While some of these are not important as factors to be considered in the selection of one antibiotic rather than the other in public health institutions where all respondents practice, some of them are indeed of considerable importance. The question of brand consideration as a factor in antibiotic selections, for example, is unimportant as prescribers in the first place prescribe generic names of antibiotics as listed in the EML and patients most of the time are served with generic products from pharmacies of respondents' hospitals, clinics or health posts.

Other factors indicated by respondents as influencing their decisions in making antibiotic choices and which are considered unimportant include factors of severity of illness, recurrence of infections and consequences of not treating an infection. While choices can be made from different formulations of a given antibiotic depending on the severity of patient's condition, the choice of what antibiotic to use in treating the patient is determined by the nature of the infection in terms of implicated bacterial pathogens and not the severity of the infection per se. Severity of illness for this reason can be a factor to consider when choices are made between different formulations of a given antibiotic but not when choices are made from a given list of available antibiotics. Empiric antibiotic prescription is not advised in recurrent infections presumably treated with antibiotics in previous incidences of the infection. Antibiotic selection in recurrent infections should be based on culture sensitivity test results or any other means of identifying causative bacterial pathogens of the infection and their sensitivities to antibiotics rather than a trial and error selection of antibiotics in further empiric treatment of the infection as respondents' use of the recurrence of infection as a factor in antibiotic selection suggests. Consequences of not treating a clinical condition with an antibiotic has to do with taking a decision as to whether or not to treat the condition with an antibiotic and not what antibiotic to use in treating the condition as respondents' use of this as a factor in antibiotic selection again suggests. Recurrence of infections and consequences of not treating given clinical conditions with antibiotics are both thus not

factors to be considered as influencing respondents' decisions in making antibiotic choices.

Sites of infections, sensitivities of patients to given antibiotics and antibiotic dosage regimens, as cited by respondents, are important factors to consider in making choices of antibiotics in treating infections. Considering site of an infection in antibiotic treatment affords a means of identifying the most probable pathogens associated with the infection and hence the selection of an antibiotic that will successfully target such pathogens. Patient antibiotic sensitivity reaction considerations are necessary in selecting antibiotics that provide maximum therapeutic benefits without exposure of patient to risks of developing allergic reactions as would be the case in the event of prescribing antibiotics to which a patient is sensitive. Dosage regimen considerations of antibiotics with similar spectra of activity and selecting one with longer dosing intervals rather than the other with shorter dosing intervals improve patient compliance to treatment with higher chances of better treatment outcomes. Indications of these factors, though made by only 13.7% (n = 7) of respondents, suggest the awareness of some respondents of their importance in appropriate prescribing of antibiotics. The large proportion of respondents [86.3% (n = 44)] not indicating these factors, however, questions respondents' knowledge of them and documents a non-adherence to them, particularly the non-consideration of sites of infection as a factor in antibiotic prescribing, as contributory to inappropriate prescribing of antibiotics

4.3.6 Determining the extent to which antibiotic stock unavailability limits respondents' ability to select antibiotics of choice (Questions 21 and 22)

The section presents results of an investigation into the extent to which unavailability of antibiotics in respondents' practice site pharmacies limit their ability to prescribe their choices of antibiotics. Questions asked specifically sought to establish the extent to which antibiotic stock outs limit respondents' abilities to make antibiotic choices and also what they actually do in situations of such stock outs.

4.3.6.1 Results

Frequency distributions of respondents according to their perceptions of the extent to which antibiotic stock unavailability limits their ability to select antibiotics of their choices

and also their indications of what they do in practice in the event of their first choice antibiotics not being available at their practice site pharmacies are shown in Tables 4.3.44, through 4.3.49. and outlined as follows:

- **The extent of limitations imposed by antibiotic stock outs to prescribers' choices of antibiotics (Tables 4.3.44 and 4.3.45)**

Of the total number of respondents,

- 7.8% (n = 4) only, claimed not being limited at all in their choices of antibiotics for the treatment of infections in the event of antibiotic stock outs in their pharmacies.
- 35.3% (n = 18) said they were limited to a minor degree by antibiotic unavailability in stock;
- 49.0% of respondents reported being limited to a major degree in their selection of antibiotics of their preference for treating infections by the unavailability of antibiotics in the pharmacy stores of their practice sites;
- A majority of 84.3% (n = 43) of respondents by summation are limited to some degree, either minor or major, in their ability to select their preferred antibiotics in treating infections. They are composed of 87.5% of (28 out of 32) and 81.9% (9 out of 11) of respondents practicing respectively in government and Christian Health Association of Lesotho (CHAL) owned health institutions. Of those practising in both private establishments and either government or CHAL owned health institutions, 75.0% (6 out of 8) were seen to indicate that antibiotic stock outs put limitations to their ability to make antibiotic choices.

Table 4.3.44 Frequency distribution of respondents by qualifications and according to degrees to which antibiotic stock outs limit choice of antibiotics (Question 21)

Degrees to which antibiotic choices are limited	Frequencies of respondents by qualifications and according to indications of degrees to which antibiotic stock outs limit choice of antibiotics.													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
Not all	1	9.1	0	0	1	4	0	0	1	50	1	50	4	7.8
Minor degree	4	36.7	0	0	10	40	3	37.5	1	50	0	0	18	35.3
Major degree	6	54.5	2	66.7	13	52	4	50	0	0	0	0	25	49
No response	0	0	1	33.3	1	4	1	12.5	0	0	1	50	4	7.8
Total	11	100	3	100	25	100	8	100	2	100	2	100	51	100

Table 4.3.45 Frequency distribution of respondents by practice types and according to degrees to which antibiotic stock outs limit choice of antibiotics (Question 21)

Degrees to which antibiotic choices are limited	Frequencies of respondents by practice types and according to indications of degrees to which antibiotic stock outs limit choice of antibiotics							
	Government owned		Christian Health Association of Lesotho owned		Private and either of both indicated ownership types		Total	
	n	n%	n	n%	n	n%	n	n%
Not all	3	9.4	0	0	1	12.5	4	7.8
Minor degree	10	31.3	4	36.4	4	50.0	18	35.3
Major degree	18	56.3	5	45.5	2	25.0	25	49
No response	1	3.2	2	18.2	1	12.5	4	7.8
Total	32	100	11	100	8	100	51	100

- **What respondents do in the event of antibiotic stock outs (Tables 4.3.46, 4.3.47, 4.3.48 and 4.3.49)**

With respect to what respondents actually do in practice in the event of their first choice antibiotics being out of stock and out of total number of respondents,

- 49.0% (n = 25) respondents said they directed patients to buy their 1st choice prescribed antibiotics. By practice types, they constituted 56.3% (18 out 32) and 27.3% (3 out of 11) of respondents from government and CHAL owned health institutions and also 50.0% (4 out of 8) of those respondents practising in both private establishments and either government or CHAL owned health institutions.
- 31.4% (n = 16) of them claimed they do not ask patients to buy their 1st choice prescribed antibiotics;
- 19.6% (n=10) failed to indicate what they did in practice when their first choice antibiotics are out of stock;
- 82.4% (42 out of 51) of them in response to the question seeking to establish whether respondents prescribe a second choice antibiotic in the event of their first choice antibiotics not being in stock indicated they prescribed a second choice of antibiotic that would be available at their practice site pharmacies;
- 5.9% (n = 3) of them said they did not prescribe a second choice antibiotic in the indicated circumstances;
- 11.8% (n = 6) refrained from answering this part of the question;
- the 82.4% indicating that they prescribed second choice antibiotics in the event of their first choice prescribed antibiotics being out of stock were composed respectively of 87.5% and 72.7% of respondents from government and CHAL owned health institutions and also 87.5% of those practicing in both private establishments and either government or CHAL owned health institutions.

Table 4.3.46 Frequency distribution of respondents by qualifications and according to response indications as to whether or not they ask patients to buy 1st choice prescribed antibiotics [Question 22 (i)]

Response indications to measures taken	Frequencies of respondents by qualifications and according to indications of whether or not they ask patients to buy 1st choice prescribed antibiotics													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	n%	n	n%	n	n%	N	n%	n	n%	n	n%	n	n%
Yes	7	63.4	1	33.3	14	56.0	1	12.5	1	50	1	50	25	49
No	3	27.3	0	0	8	32.0	5	62.5	0	0	0	0	16	31.4
No Response	1	9.1	2	66.7	3	12	2	25.0	1	50	1	50	10	19.6
Total	11	100	3	100	25	100	8	100	2	100	2	100	51	100

Table 4.3.47: Frequency distribution of respondents by practice types and according to response indications as to whether or not they ask patients to buy 1st choice prescribed antibiotics [Question 22 (i)]

Degrees to which antibiotic choices are limited	Frequencies of respondents by practice types and according to indications of whether or not they ask patients to buy 1st choice prescribed antibiotics							
	Government owned		Christian Health Association of Lesotho owned		Private and either of both indicated ownership types		Total	
	n	n%	n	n%	n	n%	n	n%
Yes	18	56.3	3	27.3	4	50.0	25	49
No	8	25.0	6	54.5	2	25.0	16	31.4
No Response	6	18.8	2	18.2	2	25.0	10	19.6
Total	32	100	11	100	8	100	51	100

Table 4.3.48 Frequency distribution of respondents by qualifications and according to response indications as to whether or not they prescribe 2nd choice in place of 1st choice prescribed antibiotics [Question 22 (ii)]

Response indications to measures taken	Frequencies of respondents by qualifications and according to indications of whether or not they prescribe 2nd choice in place of 1st choice prescribed antibiotics													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	n%	n	n%	n	n%	N	n%	n	n%	n	n%	n	n%
Yes	11	100	2	66.7	20	80.0	7	87.5	1	50	1	50	42	82.4
No	0	0	0	0	2	8.0	0	0	1	50	0	0	3	5.9
No Response	0	0	1	33.3	3	12	1	12.5	0	0	1	50	6	11.8
Total	11	100	3	100	25	100	8	100	2	100	2	100	51	100

Table 4.3.49: Frequency distribution of respondents by practice types and according to response indications as to whether or not they prescribe 2nd choice in place of 1st choice prescribed antibiotics (Question 22 (ii))

Degrees to which antibiotic choices are limited	Frequencies of respondents by practice types and according to indications of whether or not they prescribe 2nd choice antibiotics							
	Government owned		Christian Health Association of Lesotho owned		Private and either of both indicated ownership types		Total	
	n	n%	n	n%	n	n%	n	n%
Yes	28	87.5	8	72.7	7	87.5	42	82.4
No	2	6.3	0	0	0	0	3	5.9
No Response	2	6.3	3	27.3	1	12.5	6	11.8
Total	32	100	11	100	8	100	51	100

4.3.6.2 Results Evaluation and Discussion

In principle prescribers would as expected of them, and according to factors they consider in selecting antibiotics from among available stock of antibiotics, prescribe antibiotics they consider most cost-effective in treating a given infection as their first choice antibiotic in treating that infection. In the event of such first choice antibiotics not being available in stock they have the option of prescribing a second choice antibiotic provided such a second choice antibiotic favourably compares to the first choice antibiotic on the basis of factors taken into consideration in selecting the first choice antibiotic. Depending on the infection being treated, antibiotic stock unavailability can pose a limitation to antibiotic selection and compromise infection treatment, particularly, if the prescriber by institutional policy has to prescribe an antibiotic from available stock in treating such an infection. Prescribers, however, have the option to insist and direct patients to obtain their first choice antibiotics from retail pharmacies if alternative antibiotics available in their practice site pharmacy stores in their opinions are not favourably comparable with their first choice antibiotics favourably. How easily a prescriber does this, however, is determined by guiding policies at his or her place of practice amidst the strength of his or her personal conviction about what antibiotic best treats the infection on hand.

- **The effect of institutional policies on antibiotic choices for prescribing**

In Lesotho and as of common knowledge health delivery policies of government entitle patients to free medications at government owned health institutions upon the payment of a nominal registration fee (Not gazetted for reference). Patients' awareness of this privilege, which they naturally interpret as a right, makes them expect to be served with every item prescribed for them at these hospitals. This would put prescribers under pressure of substituting their preferred drugs for treating patients' ailments, including antibiotics, with second choice drugs that may be available at practice site pharmacies.

The policy in CHAL hospitals at the time of data collection, also of common knowledge, was one according to which patients pay for their prescribed medications and hence can be considered more willing to purchase their first choice antibiotics when asked to do so, in the event of antibiotic stock outs. Even then prescribers, when informed by a pharmacy of the unavailability of first choice prescribed antibiotics like the government

health institutions, do prescribe second choice antibiotics which the pharmacies may be having in stock. In such instances however, expectations are that prescribers would be under less pressure, secondary to workplace policies on drug prescribing, to necessarily prescribe drugs that are available in stock at their practice site pharmacies. Prescribers for this reason, are seen to be more easily inclined towards prescribing antibiotics that best treat infections on hand. Here again, the tendency to do this would be much determined by the strength of the prescribers' conviction that his choices of an antibiotic would be that which will treat infections effectively.

By provisions of clause 3.1.6 of a new memorandum of understanding between Government of Lesotho and CHAL which took effect from January 1st 2008, patients like those seeking medical attention from government owned institutions, now pay a nominal fee for services, including drug treatment, at CHAL owned institutions (Government of Lesotho & The Christian Health Association of Lesotho., 2007: 7).

- **Assessing the extent to which antibiotic stock outs pose problems to prescribers' choice of antibiotics**

The results of this investigation are intended to establish the extent to which antibiotic stock outs pose problems to prescribers' choices of antibiotics which in their opinions are most appropriate in treating infections they diagnose in patients. They are also intended to establish how in practice such problems are addressed to achieve best treatment outcomes. Respondents' expression of the terms minor and major degrees as measures of the extent to which unavailability of antibiotics would limit their ability to select antibiotics indicates the existence of the problem at study sites. This is without giving any specific interpretation as to what it entails when respondents say antibiotic stock outs limit their abilities by these degrees of measure. As many as half the total number of respondents reported that antibiotic stock unavailability limited their ability to select their choices of antibiotics to a major extent (Table 4.3.44). It is reported as a problem at equally high rates of 87.6% and 81.9% respectively at both government and CHAL health institutions (Table 4.3.45) and makes antibiotic stock outs as a major factor that has the potential of limiting prescribers' ability to prescribe antibiotics appropriately.

Results of outpatient prescription analysis in study Phase I of this research reported only 2.4% of the total of prescriptions analysed as prescriptions for which second choice

antibiotics were dispensed (Section 4.1.2.3). Almost all antibiotic prescriptions assessed (97.6%) were dispensed for first choice antibiotics. Logically, this result did not identify antibiotic stock outs as a major problem that significantly limited prescribers' ability to select antibiotics appropriate for treating infections. However, since data for Phase I of the research were collected for a period of one-month only, it could be assumed for explanation purposes that, for whatever reason, antibiotic stock outs were not a problem at study sites during that one month period of data collection for that phase of the research. On this basis, the high percentage of respondents asserting that antibiotic stock outs posed limitations to their antibiotic selection ability according to results of this questionnaire survey, would be taken as what rather reflects the general situation and discussed as such.

- **Assessing the impact of problems of antibiotic stock outs on prescribers' choices of antibiotics and the appropriateness of antibiotic prescriptions**

Prevailing policies in serving prescriptions at government health institutions as mentioned above is considered a driving force that may compel prescribers in some instances, to prescribe second choice antibiotics that may not necessarily compare favourably in activity to first choice antibiotics. This particularly could happen in situations of prescribers lacking strong convictions about the purposes and therapeutic effectiveness of their first choice antibiotics. Respondents indicating that antibiotic stock unavailability does not limit in any way their abilities to prescribe antibiotics, may be indicative of prescribers in this category. They comprise respondents in both nursing and medical practitioner qualifications (Table 4.3.45).

Respondents claiming that antibiotic stock outs limited their ability to make antibiotic choices to "minor" extent represented the subgroup of respondents indirectly acknowledging the existence of the problem but always managing to do something about it when it arose. Such respondents were most likely to prescribe alternative antibiotics which by their judgement were almost always comparable in efficacy to their first choice antibiotics. Their admission of the minor limitation the problem posed on their antibiotic selection ability indicated their readiness to substitute one antibiotic for the other without reservation and perhaps any serious comparison between their first and alternative second choice antibiotics. Similar to the category of respondents who said the problem of antibiotic stock outs did not limit their ability to select antibiotics, this

category of respondents was also seen not to have strong convictions about their first choice antibiotics being antibiotics that would treat infections they prescribed them for most cost-effectively. Respondents in this category represent 35.3% of the total number of respondents composed of almost equal percentage distributions of 31.3% and 36.4% in both government and CHAL health institutions (Table 4.2.45). Together with respondents who said the problem of antibiotic stock outs did not limit their ability to select antibiotics, they represented 43.1% of the total number of respondents. Characteristically they can be described as a group of prescribers who are seen to exhibit a considerably high degree of lassitude in their selection of antibiotics in treating infections. They have approximately equal percentage distributions of 40.6% and 36.4% in both government and CHAL health institutions (Table 4.2.45).

The subgroup of respondents indicating that antibiotic stock outs posed major limitations to their ability to make antibiotic choices were taken to represent the category of prescribers who were about strong convictions of their first choice antibiotics being antibiotics that were most likely to treat successfully infections they prescribed them for. This is inferred by interpretations of the expression of "major" as a high degree of difficulty respondents have in accepting equality in efficacy between their first choices and alternatively selected second choices of antibiotics. This category of respondents was most likely to prescribe antibiotics appropriately for the treatment of given infections. They are also the most likely of respondents who will insist on their first choice antibiotics being obtained by their patients by all means, even if that would mean they would have to purchase them from retail pharmacies. They represented 49.0% of the total number of respondents and included respectively 56.3% and 45.5% of respondents from both government and CHAL health institutions (Table 4.3.45).

The proportions of 43.3% and 49.0% of respondents respectively adjudged as having weak and strong convictions of the efficacy of their first choice antibiotics in treating infections they prescribed them for, predicted these percentage proportions as the respective percentage proportions of respondents who most readily prescribe second choice antibiotics or direct patients to buy their first choice antibiotics. Results indeed indicated 49.0% of respondents who indicated they did direct patients to purchase their first choice antibiotics from retail pharmacies as against 31.4% who said they did not and 19.6% who did not respond to the questions (Table 4.3.46). As many as 56.3% of the

49% of respondents who said they directed patients to buy their first choice antibiotics came from government health institutions as against a reported 27.3% coming from CHAL health institutions (Table 4.3.47). The higher percentage proportion of respondents saying that they directed patients to buy their first choice prescribed antibiotics coming from government hospitals portrays a pattern that shows more unwillingness on the part of prescribers from government than CHAL health institutions to prescribe second or alternative choices of antibiotics. This is contrary to what I has been expected taking into account what effects government policies of free drug supply to patients will have on antibiotic prescribing in government health institutions as speculated in an earlier paragraph. It was thought that in CHAL health institutions where the practice of patients paying for their medications prevail, prescribers would be better placed to convince their patients to buy antibiotics of their first choices if they were strongly convinced of the therapeutic efficacies of such first choice antibiotics in treating infections for which they prescribed them.

This observed tendency of prescribers in CHAL health institutions being more inclined towards prescribing second choice antibiotics in situations of first choice antibiotics being out of stock as compared to the observed situation in government hospitals, may be explained on the basis of sources of drug financing in both types of institutions at the time of data collection, assuming firstly that the observed trend is substantive. Drug budgets in CHAL health institutions are financed from income generated by the institutions themselves as opposed to government institutions which are financed by government. In CHAL health institutions there is bound to be a natural inclination towards patients being made to buy what drugs these institutions have in stock in order to generate the funding needed for drug stock replenishment. This is seen as creating an institutional pressure on prescribers to substitute first choice prescription drugs, antibiotics inclusive, in the event of their first choice being out of stock. In the case of antibiotics possibilities are that alternative choices of the drugs may not always not be the most appropriate for treating indicated infections and as such be detrimental to appropriate antibiotic selection for effective treatment of infections.

Respondents' indications of directing patients to buy their first choice antibiotics, as results indicated and as discussed above did not reflect in their responses when asked directly whether they prescribed second choice antibiotics or not. A majority of 82.4% of

respondents said they prescribed second choice antibiotics (Table 4.3.48), with 87.5% and 72.7% of the respective numbers of respondents coming from government and CHAL health institutions (Table 4.3.49). It was expected that the 49.0% of respondents who said they directed their patients to buy their first choice antibiotics would respond negatively to the question asking them directly as to whether or not they prescribed second choice antibiotics in situations of their first choice not being available. The failure of this subgroup of respondents to respond to this question in the expected way suggests that respondents' indications of directing patients to buy their first choice antibiotics is only an expression of what they think should be the better option to take in the interest of the patient This will be so particularly if they are strongly convinced of their first choice antibiotics being what would most appropriately treat diagnosed infections. In practice prescribers are seen to be more prone to prescribe second choice antibiotics compared to their directing patients to buy first choice prescribed antibiotics.

From the forgoing discussions, the prescribing of second or alternative choices of antibiotics to substitute prescribers' first choices of the drugs in the event of their not being in stock is inferred as the norm in the established patterns of antibiotic prescribing at all study site hospitals irrespective of whether they are government or CHAL owned. The practice is postulated to be largely driven by institutional policies and is also viewed as fomenting inappropriate prescribing of antibiotics. This view makes an exception of situations where prescribers are able to justify the appropriateness of antibiotic substitutions by establishing the existence of similarities in the therapeutic efficacies of first and alternative choice antibiotics based on their knowledge of the antimicrobial properties of the agents. Use of procedures in selecting first and alternative choices of antibiotics as developed and shown in Section 4.2.4 may offer a solution to the problem of prescribers' dilemma of antibiotics to prescribe in substitution for their first choice antibiotics.

4.3.7 Investigating reasons for prescribers' not requesting for information on the morphological characteristics of target bacterial pathogens as basis for empiric antibiotic prescribing (Questions 23, 24 and 25)

The section presents results of investigation into the extents and reasons for prescribers' use or non-use of laboratory provided information on the morphological characteristics of target bacterial pathogens as basis for empiric antibiotic prescribing. Data records of

respondents with laboratory facilities at their practice sites only were analysed. Two main investigating questions dealing with time period within which respondents received feed-backs from laboratories after sending specimens for examination and reasons why some respondents dissented adherence to the principle of seeking to know microscopic characteristics of infecting pathogens before initiating antibiotic therapy were investigated. Results were evaluated and discussed from a perceptive that sought to identify factors negating respondents' no- adherence to the principle.

4.3.7.1 Results

Tables 4.3.50, 4.3.51 and 4.3.52 respectively show percentage frequency distributions of indicated categories of respondents according to

- their indications of whether or not they requested for rapid microscopic identification or gram's stain characteristics of bacterial pathogens before antibiotic therapy initiation;
- their practice sites and time lengths of receiving feed-backs from laboratories when they requested for rapid microscopic identifications of bacterial pathogens;
- time lengths within which laboratories made available results to those requesting for rapid microscopic identification of gram-stain characteristics of bacterial pathogens before antibiotic therapy initiation; and
- reasons why they did not request for information on microscopic identification or gram stain characteristics of bacterial pathogens before antibiotic therapy initiation.

Of a total 37 respondents with laboratory facilities,

- 51.4% (n = 19) respondents with laboratory facilities claimed that they requested for microscopic identification and gram-stain characteristics of bacterial pathogens prior to their empiric prescription of antibiotics;
- 27.0% (n = 10) said they did not request for information on morphological and gram stain characteristics of infecting bacterial pathogens prior to their initiation of antibiotic therapy; and
- 21.6% (n = 8) of respondents did not respond to the question.

Table 4.3.50 Frequency distributions of respondents with laboratory facilities according to their indications of whether or not they request for rapid microscopic identification or Grams stain characteristics of bacterial pathogens before antibiotic therapy initiation (Question 23)

Response indications	Frequencies of respondents by qualifications and according to whether or not they request rapid microscopic identification of bacterial pathogens before antibiotic therapy initiation.													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%	n	n%
Yes	6	54.5	2	66.7	11	47.8	0	0	0	0	0	0	19	51.4
No	3	27.3	0	0	7	30.4	0	0	0	0	0	0	10	27.0
No Response	2	18.2	1	33.3	5	21.7	0	0	0	0	0	0	8	21.6
Total	**11**	**100**	**3**	**100**	**23**	**100**	0	0	0	0	0	0	**37**	**100**

Table 4.3.51 Frequency distributions of respondents indicating they make requests for microscopic identification of infecting pathogens according to their practice sites and time lengths of receiving feed-back from laboratories (Question 24)

Time	Frequencies of respondents by practice sites and according to whether or not they request rapid microscopic identification of bacterial pathogens time lengths of receiving fee- backs from laboratorie											
	Berea		Maluti		Motebang		Queen II		Scott		Total	
	n	n%	n	n%	N	n%	n	n%	n	n%	n	n%
0-3 hrs	0	0.0	3	75.0	1	20.0	0	0.0	0	0.0	4	21.1
3 - 8 hours	1	100	0	0.0	0	0.0	1	14.3	0	0.0	2	10.5
> 8 hours	0	0.0	0	0.0	2	40.0	3	42.9	0	0.0	5	26.3
No feed back	0	0.0	1	25	2	40.0	3	42.9	2	100	8	42.1
Subtotal (> 8 hrs + no feed back)			**1**	**25**	**4**	**80.0**	**6**	**85.8**	0	0.0	**13**	**68.4**
Total	**1**	**100**	**4**	**100**	**5**	**100**	**7**	**100**	**2**	**100**	**19**	**100**

Table 4.3.52 Frequency distributions of respondents who do not request for microscopic identification or Gram stain characteristics of bacterial pathogens prior to prescribing antibiotics according to reasons for not requesting for such information (Question 25)

Reason	Frequencies of respondents according to reasons for not making request.	
	n	% n
Not feasible because of large number of patients	4	40.0
Clinical experience adequate to guide in antibiotic selection	0	0
Not cost-effective in patient management	1	10
Results not made available in time to aid decision	5	50.0
Other reason	0	0
Total	10	100

Of a total number of 19 respondents claiming that they requested for microscopic identification and gram-stain characteristics of bacterial pathogens prior to their empiric prescription of antibiotics,

- 21.1% (n = 4), indicated they received feed-back from laboratories within three (3) hours of sending specimens to the laboratory. Three out of four (3 out of 4) of such respondents came from Maluti hospital and one (1) from Motebang hospital;
- 10.5% (n = 2) indicated receiving feed-backs within 3 - 8 hours. One each of such respondents came from Berea and Queen II hospitals; and
- A majority of 68.4% (n = 13) claimed results either were made available to them in more than 8 hours time or never made available to them at all.

Of the total number of 10 respondents who said they never requested for microscopic identification and gram-stain characteristics of bacterial pathogens prior to their empiric prescription of antibiotics,

- 40.0% (n = 4) supported their dissent to this principle by indicating that it was not feasible for them to request for such information prior to their initiation of antibiotic therapy because of the large number of patients they saw and treated;

- 50.0% (n = 5) gave reasons of results not being made available to them in time to aid their decision making on treatment options even if they had made the request;
- 10% (n = 1) indicated adherence to the principle of requesting for such information prior to their initiation of antibiotic treatment not being cost-effective in patient management;
- no respondent in the category agreed to the adequacy of their clinical experience being a guide to their selection of antibiotics in treating infections as a reason for not finding it necessary to request for microscopic identification of infecting bacteria before initiating antibiotic therapy or gave any other reason for ignoring this principle in antibiotic prescribing.

4.3.7.2 Results Evaluation and Discussion

With the exception of cases where a prescriber may have good knowledge in identifying bacteria types associated with an infection at a given body site, requesting for rapid microscopic identification of likely bacterial pathogens causing an infection may be the only means by which prescribers may have an idea of bacterial pathogens implicated in a given infection Indicating the importance of this in appropriate antibiotic therapy, Archer and Polk (2005:795) stated that a basic tenet of antibiotic therapy include when appropriate material containing the infecting organism(s) is obtained before the start of treatment so that presumptive identification of infecting pathogen(s) can be made by microscopic examination of stained specimens to allow for the selection of antibiotic(s) that appropriately target said infecting pathogen(s). In principle therefore, prescribers are expected to send, where appropriate, specimens of materials from sites of infection to laboratories and request for microscopic identification of assaulting pathogens to enable them select antibiotics that would appropriately target them in the empiric treatment of these infections.

Results as presented above have shown 51.4% of respondents with laboratory facilities saying they requested for rapid morphological identification and grams stain characteristics of bacteria pathogens before starting antibiotic therapy in patients. This is against a total 48.6% of respondents who either categorically said they did not request

for rapid morphological identification and Gram stain properties of bacterial pathogens before starting antibiotic therapy in patients [27.0% (n = 10)] or desisted from answering the question [21.6% (n = 8)] (Table 4.3.50). The almost half (48.6%) proportion of the subgroup of respondents seemingly failing to adhere to the principle when considered against the impact of adherence to the principle on appropriateness of antibiotic prescribing for inpatients as discussed in Section 4.3.3 (Question 11), is predictive of high rates of inappropriate empiric prescribing of antibiotics among the patient group. The majority of prescribers were seen to lack the knowledge base required for the appropriate selection of antibiotics in the empiric treatment of infections as results of the knowledge test aspect of the survey showed (Section 4.3.5).

- **Factors that contribute to prescribers' failure to request for laboratory assisted presumptive identification of infecting pathogens prior to antibiotic prescribing**

Factors likely to contribute to prescribers' failure to request for rapid microscopic identification of pathogens before initiating antibiotic therapy may either be attributed to behavioural attitudes in antibiotic prescribing on the part of the prescribers themselves or operational deficiencies of laboratories serving the health institutions. Percentage frequency distributions of respondents according to time lengths within which they received results for requests to the laboratories or reasons they gave as preventing them from requesting for this laboratory service before prescribing antibiotics provide insights to what these factors are. Prescriber behavioural attitudes in antibiotic prescribing may be fostered by other factors including conditions under which prescribers practice or even the culture of medical practice within facilities where prescribers practice their professions. These are speculative though, and needs enlightenment by further studies to become substantive.

The time factor with regard to when to start antibiotic treatment in patients and hence how long prescribers may have to wait for laboratory generated information enabling them to start such treatment is crucial and is a major issue that needs consideration when patients are managed for infections. Antibiotic treatment of infections should under ideal situations commence immediately as soon as the presence of the infection has been diagnosed. The seriousness of the infection, however, can be a determining factor as to how soon antibiotic treatment can be started or how long prescribers for that matter

have to wait for results of rapid laboratory investigations establishing the morphological characteristics of bacterial pathogens implicated in the infection, before commencing treatment. In this study, a waiting time period equal to or less than 3 hours for prescribers to wait and obtain results of rapid laboratory investigations establishing the morphological characteristics of bacterial pathogens implicated in infections is considered tangibly appropriate. A waiting time period of between 3 - 8 hours may be acceptable only in situations where the infection is less serious. Waiting time periods greater than 8 hours is totally unacceptable in much the same way as situations in which results are never received from laboratories. This in the opinion of the researcher will discourage prescribers from requesting for such rapid laboratory investigations prior to their commencement of treatment.

Results as indicated above have shown that as many as 26.3% of respondents who claimed they requested for rapid microscopic identification of bacterial pathogens received results 8 hours or more after they had made such requests. A still higher percentage proportion of 42.1% never received feed-back. This gave a total of 62.5% of respondents who requested for such tests to aid in their selection of antibiotics in empiric antibiotic treatment assumingly dissatisfied with services they got from their respective practice site laboratories. Implications are that this group of respondents would become disillusioned with the operational systems of their laboratories and may be reluctant to request for such tests. This assumption in a away is confirmed to be true by the high 50.0% of the respondent group dissent to the principle giving reasons of results not being made available in time as the cause of their failure to request for this information to aid decisions they make as they prescribed antibiotics for their patients. This identifies and establishes deficiencies in the operational systems of microbiology laboratories at study sites as a major factor contributing to respondents' disinterest in requesting for rapid microbial identification before initiating antibiotic treatments.

Large percentage proportions (80% to 100%) of respondents from Scott, Motebang and Queen II hospitals claimed that feed-back to their requests for rapid microscopic identification were made available to them in more than 8 hours' time or never made available to them at all. Microbiology laboratories in these hospitals in that order were seen by this result to be least efficient in making results of microscopic investigations available to medical staff. Seventy-five per cent of respondents from Maluti hospital,

indicated getting feed-back on their requests for microscopic identification of infecting pathogens within 0 to 3 hours. Comparably this has illustrated the microbiology laboratory at this site hospital to be more efficient in the respect of making results available to medical staff than those of the aforementioned study site hospitals (Table. 4.3.51).

Heavy workload in terms of number of patients that respondents treat on daily basis was cited by as many a 40.0% of respondents who did not routinely request for rapid microscopic identification of infecting bacteria before initiating antibiotic treatments. Respondents' workload has been investigated and results discussed in Section 4.3.1. The majority of respondents saw more than 60 patients daily which is significantly higher than the internationally acceptable workload of about 26.4 patients per day according to Raymont *et al.* (2005: 4 and 6 of 9). The direct effect of such a heavy workload is seen as a reduction in patient - prescriber contact time needed for diagnostic including laboratory investigations. Presumably, this has the potential of compromising the efficiency and output of medical personnel and has in this study surfaced as a reason of some respondents not being able to request for rapid microbial identification of morphological characteristics of bacterial pathogens prior to antibiotic prescribing. To a large extent therefore, prescribers' workload has been identified as a major contributing factor to majority of prescribers' failure to request for and use laboratory provided information on morphological characteristics of bacterial pathogens in appropriate selection of antibiotics for effective empiric treatment of infections. Viewed from this perspective, the factor of heavy workload is seen as contributing significantly to inappropriate prescribing of antibiotics.

Interestingly no respondent cited adequacy of his/her clinical experience as providing the guidance they needed in antibiotic selection and giving it as a reason for disinterest and failure to request for microscopic identification of infecting bacteria before initiating antibiotic therapy. This by interpretation means respondents' acknowledgement of the fact that dependence on one's clinical experience alone is not a sufficient means of diagnosing and treating infections and that other procedures are equally important and can be used together with clinical experience in the appropriate diagnosis and treatment of infections. It suggests that respondents who for whatever reason were seen not to be prepared to use laboratory facilities at their disposal to aid in their diagnosis and

treatment of infections, may still be receptive to measures taken to improve appropriateness of antibiotic prescribing. While these may include revamping the operational system of laboratories with improved procedures in laboratory results reporting particularly to obliterate the resentment of prescriber's use of the facilities as results of this study purport, the introduction and use of antibiotic selection procedures as developed by this study (Sections 3.5.2 & 4.2.4) is predicted to be highly welcomed by prescribers.

4.3.8 Determining the extent of respondents' need for antibiotic prescribing guidelines and refresher causes

The section presents results of an assessment of respondents' need for antibiotic prescription guidelines to aid in their diagnosis and treatment of infections. The questions of whether or not treatment guidelines and education of prescribers in antibiotic prescribing would have a positive impact on the prescribing and use of antibiotics as reviewed in the literature and whether the introduction of these measures as a means of improving antibiotic prescribing in Lesotho were addressed in ensuing results evaluations and discussions.

4.3.8.1 Results

Frequency distribution of respondents according to their qualifications and perceptions on their needs for antibiotic prescription guidelines and refresher courses in antibiotic prescribing are shown in Tables 4.3.53 and 4.3.54 and outlined as shown below. Of all 51 respondents who participated in the study,

- majority 86.3% indicated their need for antibiotic prescription guidelines. A total of 82.4% of respondents again made up of high percentage proportions of respondents of all qualification categories expressed their need for refresher courses in antibiotic prescribing;.
- equal percentage proportions of respondents qualified their degrees of need by indicating that they "need it" (41.2%) and "need it very much" (41.2%);
- 11.8% of respondents comprising all qualification categories with the exception of registered nurses and nursing assistants indicated they did not need any refresher courses; and
- 5.9% (n = 3) of respondents did not respond to the question.

Table 4.3.53. Frequency distribution of respondents according to their qualifications and perceptions on need for antibiotic prescription guidelines.

Response indications	Frequencies of respondents by qualifications and according to indications of whether or not they need antibiotic prescription guidelines													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	n%	n	n%	N	n%	n	n%	n	n%	n	n%	n	n%
Yes	9	81.8	2	66.7	23	92	6	75	2	100	2	100	44	86.3
No	1	9.1	0	0	2	8	0	0	0	0	0	0	3	5.9
No Response	1	9.1	1	33.3	0	0	2	25	0	0	0	0	4	7.8
Total	11	100	3	100	25	100	8	100	2	100	2	100	51	100

Table 4.3.54. Frequency distribution of respondents according to their qualifications and perceptions on need for refresher courses in antibiotic prescribing.

Response indications	Frequencies of respondents by qualifications and according to indications of whether or not they need antibiotic prescription guidelines													
	Physician specialists		Surgical consultants		General practitioners		Nurse clinicians		Registered nurses		Nurse assistants		Total	
	n	n%	n	n%	N	n%	n	n%	n	n%	n	n%	n	n%
Don't need it	2	18.2	1	33.3	2	8	1	12.5	0	0	0	0	6	11.8
Need it	6	54.5	0	0	15	60	0	0	0	0	0	0	21	41.2
Need it very much	2	18.2	1	33.3	8	32	6	75	2	100	2	100	21	41.2
No response.	1	9.1	1	33.3	0	0	1	12.5	0	0	0	0	3	5.9
Total	11	100	3	100	25	100	8	100	2	100	2	100	51	100

4.3.8.2 Results Evaluation and Discussion

Guidelines, according to Nathwani *et al.* (2001:729) and Brown (2002:588) are systematically developed statements that are developed to assist practitioners and patients in making decisions about health care for specific clinical circumstances. As an analogy to this definition, antibiotic prescribing guidelines can be considered as a set of statements developed to assist practitioners in making the right decisions in their choices and dosing of and the need for antibiotics appropriate in the treatment of given infections while avoiding the development or even reducing levels of resistant pathogens to antibiotics. Considered on the basis of this definition and to achieve its purpose of ensuring that antibiotics are appropriately prescribed, it is important for antibiotic prescribing guidelines to be developed based on principles of appropriate antibiotic prescribing and knowledge of local antibiotic sensitivity patterns of bacterial pathogens. Such guidelines may also have to be integrated, where appropriate, with diagnostic algorithms of infections to ensure that prescribers make the right choices of antibiotics for established infections.

Use of clinical guidelines, including antibiotic prescribing guidelines in particular, is becoming increasingly popular as a means of influencing clinicians' practice (Brown, 2001:587) and improving antibiotic prescribing. Some surveys, according to the author, showed that guidelines have had a limited impact in terms of changing prescribers' clinical behaviour while others demonstrated that when developed, disseminated and implemented appropriately they improved clinical practice resulting in health gains (Brown, 2001:588). In the specific case of antibiotic prescribing guidelines for various infectious diseases, improvement in clinical practice and consequent health gains would expectedly demonstrate as improved treatment outcomes and possibly reduction in the development of resistant strains of pathogenic bacteria. Appropriate prescribing of antibiotics as results of study Phase I showed (Section 4.1.1.2), has been demonstrated to have a positive impact on treatment outcomes and costs of antibiotic treatments. Lemmen *et al.* (2000:384), studying the influence of an infectious disease service on clinicians' antibiotic prescribing behaviour and selection of multi-resistant pathogens, adopted a method in which they implemented treatment guidelines for most of the prevalent infections. Their aim was to optimise antibiotic usage and prescription patterns in the neurologic intensive care unit. Their findings showed that the infectious disease service through its implementation of treatment guidelines optimised antibiotic usage

and decreased as a result, the occurrence of multi-resistant gram-negative pathogens and *Candida* spp in the intensive care unit. They also reported costs being saved on antibiotic treatments at the same time. Ball *et al.* (2002:34) also indicated that in hospitals and other institutions decreased antibiotic use may reduce the prevalence of bacterial pathogen resistance as a result of successful implementation of antibiotic prescribing guidelines. They gave the example of Finland where implementation of such guidelines resulted in reduced macrolide consumption and the prevalence of erythromycin-resistant group A streptococci.

Despite the above and other evidences from the literature that testified to the beneficial effects of the use of treatment guidelines on antibiotic prescribing, prescribers' non - adherence to treatment guidelines has been identified as a problem and a matter of concern in successful implementation of treatment guidelines. Van de Beek *et al.* (2002:663) in a study in which they investigated the use of national antibiotic treatment guidelines in the treatment of adult bacterial meningitis in the Netherlands found that only 33% of patients received treatment in compliance with the guidelines, an equivalence of only a third of physicians adhering to recommendations in the guidelines. The researchers qualified this as a poor adherence to the guidelines. Collini *et al.* (2007:552 & 553) also studied the extent of prescribers' adherence to treatment guidelines for community-acquired pneumonia (CAP). They showed in their study that prescribers in an acute medical assessment unit of the Royal Liverpool University Hospital exhibited poor adherence to a British Thoracic Society's (BTS) antibiotic treatment guidelines before and even after the introduction of an educational programme in which an overview and importance of the BTS CAP guidelines were discussed. In a study in which they investigated the prescribing of antibiotic choices junior doctors make in common infections in two UK national health service (NHS) regions (Edinburgh and Newcastle-upon-Tyne NHS hospitals), Ali *et al.* (2006:961) found a low adherence rate of 41% to local hospital guidelines among doctors in Edinburgh NHS hospitals as against a rather comparatively high rate of 83% among Newcastle doctors.

Various reasons have been given in explanation of prescribers' poor adherence to antibiotic treatment guidelines by many researchers and they are worth considering in the event of an envisaged introduction of such guidelines in an attempt to improve antibiotic prescribing in Lesotho. Van de Beek *et al.* (2002:663) attributed the reason for

the Dutch prescribers' poor adherence to the guidelines as being due to the type of guidelines which was national in design and implementation, probable lack of effective dissemination and the fact that individual doctors have to decide which antibiotic to prescribe despite the availability of treatment guidelines. National guidelines in the researchers' opinion are often of limited efficacy because medical practices according to them and also to Brown (2002:590), are most often locally driven. In the Netherlands where van de Beek *et al.* carried out their study, more than than 70% of hospitals were seen to have their own antibiotic treatment guidelines. Guidelines are more likely to be adopted if users participate in their development which could happen in the development of local but not national guidelines (Brown, 2002:590). Simply publishing guidelines without effective dissemination according to van de Beek *et al.* (2002:665) has been associated with low rates of compliance.

Dissemination as defined by Brown (2002:589) is the process of bringing guidelines to the attention of their intended users with the aim of increasing awareness and influencing knowledge, attitude and behaviour and according to the author it can be achieved in many ways that include for example publication in journals, newsletters local reports, junior doctors' handbooks and direct mailing to relevant practitioners. The recognition of dissemination as an important factor determining prescribers' compliance to guidelines directly acknowledges its objective of influencing prescribers' knowledge, attitude and behaviour as indicated above, and hence education of prescribers on treatment guidelines, as important in the successful implementation of guidelines or prescribers' compliance with them. According to Brown (2002:589), active educational interventions such as seminars that are devoted exclusively to the guidelines and where potential users are given the opportunity to discuss them are more likely to be effective than didactic lectures or simply including the guidelines as part of an educational programme.

Many studies have shown that education at an individual or small group level and peer education are effective strategies to change prescribers' antibiotic prescribing behaviour and promote appropriate antibiotic prescribing in clinical set-ups. Hennessy *et al.* (2002:1544 &1547), in a study in which they investigated the effect of educational intervention on changes in antibiotic prescribing practices and its possible effect on penicillin susceptibility of nasopharyngeal *S. pneumoniae* among Alaskan natives,

demonstrated that education can substantially decrease antibiotic use overall and the use of antibiotics to treat respiratory infections. The educational programme in the study was conducted through workshops and targeted community health aides and physicians at the regional health hospitals. It had the goal of promoting understanding of upper respiratory tract infections and the appropriate indications of antibiotic therapy among indicated target beneficiaries of the programme. McNutty *et al.* (2000:497), in a similar research in which they investigated the effect of education of prescribers in antibiotic prescribing in West Gloucestershire, in the UK showed that practice-based education directed specifically at antimicrobial use can rationalise antibiotic prescribing and reduce the use of broad spectrum antibiotics which may in turn help to reduce the emergence of multi-drug resistant bacteria. The educational programme which took the form of microbiology tutorials with references to antibiotic prescribing guidelines which were distributed to participants was directed at small groups of general practitioners and was facilitated through the conduction of workshops. In yet another study in which Apisarnthanarak *et al.* (2006:768 & 774) investigated the impact of education and an antibiotic control programme on antibiotic prescribing practices, antibiotic consumption, antimicrobial resistance and costs of antibiotics in a tertiary care hospital in Thailand, it was established that an educational programme and antibiotic management programme can be associated with significant alterations of prescribing practices and reductions in antibiotic use, bacterial resistance and costs.

The above review of the literature has generally established that to a significant extent prescribers can be compliant to well-developed and appropriately disseminated antibiotic treatment guidelines and that successful implementation of such guidelines can and do exercise a positive impact on appropriate antibiotic prescribing. Education of prescribers on antibiotic prescribing particularly if disseminated through workshops can result in positive alterations prescribers' antibiotic prescribing practices with reductions in consumption of antibiotics, and development of resistance of pathogens to commonly prescribed antibiotics. Results of assessment of prescribers' need for antibiotic prescribing guidelines and refresher courses in antibiotic prescribing showed that more than 80.0% of respondents constituted by high percentage proportions of all qualifications of respondents would want to be guided in antibiotic prescribing through the use of antibiotic treatment guidelines. It also demonstrated respondents' enthusiasm on being educated on aspects of antibiotic prescribing through the presentation of

refresher courses. Taken at their face value these results can be interpreted as an admission on the part of respondents that deficiencies do exist in their antibiotic prescribing capabilities and that such deficiencies could be addressed positively through continuous education programmes and use of antibiotic prescription guidelines. General practitioners and nurse respondents, with 92.0% and between 75.0% and 100% of their numbers respectively are considered as demonstrating great enthusiasm of their needs for guidelines and continuous education programmes in antibiotic prescribing. Compared to physician specialists in particular, they are seen to be more willing to adopt measures of antibiotic prescribing guidelines or educational programmes if these are introduced as means of improving antibiotic prescribing in Lesotho. Nathwani *et al.* (2001:731) published a paper on whether or not guidelines for community-acquired pneumonia would improve the cost-effectiveness of hospital care. They observed in this paper, and accordingly indicated, that experienced physicians were the least likely to adhere to treatment guidelines and that guidelines might be most influential when clinicians were less experienced and/or lack a dominant practice style. This observation by the researchers is reflected in the pattern of respondents' expressions of willingness to comply with antibiotic prescribing guidelines or participate in educational programmes in antibiotic prescribing if these are introduced. General practitioners and nurse clinicians form the majority of prescribers in Lesotho as results of analysis of respondents demographic data showed (Figure 4.3.1). Taking this into consideration, indications of almost all respondents in the general practitioner and nurse clinician qualification groups can be taken as predictive of successful implementations of antibiotic prescribing guidelines if these are appropriately introduced. Multifaceted methods that will ensure prescribers' familiarity with and understanding of the demands of the contents of such a guideline are for this purpose recommended. In their review dealing with implementing practice guidelines for appropriate antimicrobial usage, Gross and Pujat (2001:II-55) confirmed from available evidence that multifaceted methods were very successfully used in implementing practice guidelines. By their findings individual methods of implementation that appeared useful included academic detailing, feedback from nurses, pharmacists, or physicians, local adaptation of a guideline and small group interactive sessions.

4.4 Limitations of the study

Study Phase I

- The criteria used in the prescription assessment procedures were based on the researcher's interpretations of data collected from patient files in the case of inpatients and also from patients' medical history booklets ("bukanas") in the case of outpatients and not by interviewing or questioning prescribers on how they came by prescribed antibiotics. Information collected from patients' files or case notes or patients' bukanas as data indicating whether or not prescriptions conform to criteria used for assessment of the appropriateness of prescribed antibiotics depended largely on how much of such information had been provided in patient files or bukanas as prescribers take and record patients' history. Prescribers may omit to record information they may consider as unimportant but which may be important data for the study. A prescriber upon physical examination of a patient, for example, may record "presence of lacerations and bruises" but may not state that such lacerations or bruises produce pus which the researcher can consider as "hall mark" of infection being established, even though they actually may be producing pus. Similarly, a diagnosis of "coughing" without any description of nature of cough or indications of other symptoms suggestive of bacterial infections of the respiratory tract limited the researchers' ability to classify an antibiotic prescription given for such a case as being prescribed for absolute bacterial infections of the respiratory tract.

- In some cases, what the researcher recorded as data indicating a given prescription's conformity or non conformity to a criterion depended on his interpretation of clinical information in case notes which may not necessarily be what the prescriber actually did to show consciously of his or her keeping to principles of antibiotic prescribing. Prescribers indicating "coughing" as a symptom in patient case notes for example, were taken as recognising the respiratory tract as a "site of infection" and prescriptions they wrote for such cases were assessed as conforming to the criteria of being written upon the prescribers' establishment of site of infections. Prescribers in such cases even though they might not be consciously indicating the symptom of coughing as a recognition or an

establishment of a site of infection, wrote prescriptions that were assessed in favour their being written according to this element of principles of antibiotic prescription being considered.

- Lack of adequate information from patient case notes on severity of infections for which antibiotics were prescribed, precluded analysis of data to establish the appropriateness of antibiotic prescriptions in respect to their use in treating patient groups with various degrees of severity of their illnesses. This limited adequate interpretation of results to determine precisely what impacts appropriate prescribing of antibiotics have on treatment outcomes, days of patient hospitalisation and costs of antibiotic treatments.

- Though the researcher developed tools that readily provided literature derived information on infections and their causative agents as well as the therapeutic and physico-chemical properties of antibiotics which were used in making informed decisions on the conformity of prescriptions to criteria used in prescription assessment, the challenge of deciding correctly as to whether or not prescriptions conformed to set criteria was seen as a limitation of the method used in the assessment of prescriptions. Inability to correctly decide on the conformity or non conformity of a prescription to such set criteria is seen as a limitation that may seriously compromise results.

- The above limitations as cited compromise to some extent the validity of data used in assessing the appropriateness of prescriptions by the methodology employed.

- Difficulty in monitoring outpatients for their responses to treatment was yet another limitation that precluded determination of treatment outcomes of antibiotic treatment in this category of patients as done for inpatients.

- Retrospective drug utilisation studies in which prescribers did not indicate clinical conditions for which they prescribe particular drugs in multiple diagnosed illnesses have the limitation of a researcher not being able to identify what drugs on given multiple prescriptions were prescribed for concurrently diagnosed illnesses. The same situation prevailed in this study in which antibiotic prescriptions were studied

In situations where multiple antibiotics were prescribed for concurrently diagnosed infections in a patient, the researcher had no means of knowing which antibiotic was prescribed for which infection. In the determination of frequencies of prescribed antibiotics in such instances the researcher each antibiotic on multiple antibiotics on prescriptions as being prescribed for each infection in cases of concurrently diagnosed infections. In this situations where it is desired to analyse data to determine frequencies of antibiotic prescribing, this becomes a limitation in the sense that prescribed antibiotics may be counted in favour infections for which they were not actually prescribed.

Study Phase II

Limitations associated with this phase of the research which may compromise the quality of data used in determining patterns of bacteria pathogen isolation from specimens and their sensitivities to antibiotics are as outlined below:

- Random determinations by study site laboratories of antibiotics used in culture sensitivity testing each time pathogens are isolated. This was seen to be done instead of following routines in which all antibiotics regularly used in treating infections of given bacteria isolates are tested against such isolates each time they are isolated. The practice gave rise to certain pathogens being tested for fewer times against certain antibiotics as compared with the frequencies of their isolation and testing against other antibiotics. Frequencies of isolations of pathogens and their testing against different antibiotics were seen by this limitation to vary greatly, making organisms' observed sensitivity or resistant patterns to various antibiotics, if compared, less definitive than would have been the case if organisms isolated were tested against all antibiotics of interest all the times.

- The identification of bacteria isolates by species or group names and the reporting of organisms' antibiotic sensitivities as such group or species characteristics. The limitation made it impossible in some cases to associate reported antibiotic sensitivity patterns to specific organisms and is thought to compromise data quality and adequate interpretation of results.

Study Phase III

The sample size of respondents to questionnaires used in this phase of the study is small and may be considered a limitation of the phase of the study. Questionnaires distributed however targeted all prescribers within the health service areas of the study site hospitals and with the high response rate of 76.1% to questionnaires obtained, results of the study phase are however considered as reflecting prevailing situations investigated.

4.5 Chapter Summary

The chapter covered basically results and results evaluations and discussions of all three phases of the study. Limitations as encountered in the conduct of research were also presented. Conclusions as drawn from results evaluations and discussions, limitations of the use of study results and also recommendations made within such limits are presented in the chapter that follows.

CHAPTER FIVE

CONCLUSIONS AND RECOMMENDATIONS

From the evaluations of results of this research and ensuing discussions thereof as presented in Chapter 4 the following are concluded on the patterns in which antibiotics are prescribed at study site hospitals and the impact such patterns have on treatment outcome and cost modalities of infection management in said hospitals. Statements of conclusions, though drawn generally from an academic perspective based on findings of the study, are hoped to provide baseline information needed in policy formulations by interested stakeholders within the health delivery system of Lesotho in antibiotic therapy to ensure derivation of optimum therapeutic benefits from the use of these drugs. They are outlined for brevity and cross referenced to paragraphs of the results and discussions chapter to enable their independent assessment by readers within the context in which discussions were made. For purposes of easy cross referencing to their origins, statements of conclusions are also grouped under subheadings phrased in wordings similar to those under which results were presented and discussed. Ampicillin as indicated in statements of conclusions refers to ampicillin and amoxycillin. In respect to their activities on which concluding statements are made, the two antibiotics are considered one and the same antibiotic (Petri, 2001:1202).

The literature had been reviewed as an integral part of this study in accordance with set objectives outlined in Section 1.3.2.1. Results of this review are presented in Chapter 2. They were also incorporated, where appropriate, in the evaluation and discussions of results of the empirical research or in support of statements made in such discussions.

Recommendations as given at the end of the chapter are based on the results of the research and are meant for serious consideration by stakeholders as they make use of findings of the study as basis for formulating policies in antibiotic prescribing and use in Lesotho. They are outlined following all sets of concluding statements drawn from results of discrete steps of the three phases in which the research was conducted.

5.1 Inferences on assessment of inpatient prescriptions

From the evaluations of results of inpatient antibiotic prescription assessment and discussions thereof the following can be inferred as conclusions drawn from

demonstrated patterns of antibiotic prescribing in inpatients departments of study site hospitals.

5.1.1 The extent of appropriate prescribing of antibiotics at study site inpatient departments [Sections 4.1.1.1 & 4.2.3.1] [Objective 1.3.1.2(i)]

- Evidenced by as many as 57.0% of inpatient prescriptions assessed being prescriptions that were inappropriately prescribed either for treatment or prophylaxis of infections, results of assessment antibiotic prescriptions from inpatient departments of all study sites have shown a relatively high prevalence of inappropriate prescribing of antibiotics.
- Possible violations of antibiotic prescribing principles occur in both surgical and medical wards showing trends of a higher frequency of occurrence in the former than in the latter ward type.
- CHAL hospitals were seen to be more disposed to writing antibiotic prescriptions appropriately in accordance with antibiotic prescribing principles than Government hospitals.
- Only 1.3% of prescriptions assessed were seen to be based on culture sensitivity tests, a result which emphatically established empiric antibiotic prescribing as a mainstay of infection treatment at study site hospitals amidst reported high resistances of many bacterial isolates to formulary antibiotics (Section 4.2.3.1).

5.1.2 The impact of appropriateness of antibiotic prescribing on treatment outcomes [Sections 4.1.1.2] [Objective 1.3.1.2(ii)]

- Appropriate prescribing of antibiotics based on principles of antibiotic prescribing in the empiric treatment of infections as observed, may have a positive impact on patients' response to antibiotic treatment, number of days spent in hospital and costs of antibiotics prescribed for treatment.
- The practice of prescribers requesting for culture sensitivity tests only after failures of initial antibiotic treatments is speculated to have a negative impact on total costs of inpatient antibiotic treatments as shown by the higher average costs of treatment of patients with antibiotics prescribed on the basis of culture sensitivity test results than those treated empirically.

5.1.3 Patterns and the impact of multiple antibiotic prescribing on treatment outcomes [Section 4.1.1.3] [Objective 1.3.1.2(iv)]

- One or two antibiotics per prescription were seen to be mostly prescribed for cases where prescribers may had doubts in bacterial infections being aetiologies of clinical conditions they treated. This implied by inference that prescribers by practice prescribed few antibiotics for cases of "just in case there is an infection" rather than on the basis of expediency in treating specific infections when the practice would be seen as prescribers' display of rationality in prescribing antibiotics.
- No convincing links between patients' recovery from infections and the number of antibiotics they were treated with had been established. However, results did indicate higher probabilities of higher numbers of antibiotics empirically used in treating infections having a positive impact on treatment outcomes if such antibiotics are appropriately prescribed and for clinical conditions in which bacterial infections seem absolute aetiologies.
- The number of antibiotics empirically used in treating infections does not matter significantly in patients' recovery from infection treatment in as much the same way as the appropriateness of the antibiotic prescriptions with which they are treated. Similarly the number of antibiotics prescribed in treatment for which selection of antibiotics was based on results of culture sensitivity tests predictably had been seen not to count in patient's response to antibiotic treatment as long as such selections are based on the activities of selected antibiotics against bacterial isolates responsible for the infection

5.1.4 Leading infections and antibiotics most commonly prescribed for their treatment at study site inpatient departments [Section 4.1.1.4] [Objective 1.3.1.2(v)]

- **Epidemiology of diagnosed infections among inpatients**
  - Respiratory tract infections, skin and soft tissue infections, gastrointestinal and genitourinary tract infections are in that order documented as four of the most prevalent types of infections commonly seen and treated among inpatients at all study site hospitals.

- Infections of the central nervous system (meningitis), bone (osteomyelitis and infected fractures) and blood (septicaemia) as well as pyrexia or fever of unknown origin are less frequently encountered.
- Deducing from rates of admitted cases of various infections the following can be inferred about epidemiological trends of infection diagnosis and treatment at study site hospitals and hence prevalence of given infections in Health Service Areas (HSAs) within which study site hospitals are situated:
  - Respiratory tract infections among inpatients were seen and treated at the Queen II hospital most prevalently.
  - Skin and soft tissue infections were predominantly diagnosed and treated at Motebang and Queen II hospitals.
  - Gastrointestinal and genitourinary tract infections were present at almost equal rates at all study site hospitals.
  - Other infections, notably central nervous system infections (meningitis), bone infections and infections of blood (septicaemia) were equally diagnosed and treated at study site hospitals but at relatively very low rates.

- **Patterns of antibiotics prescribing in inpatient departments at study sites**

  Antibiotics commonly prescribed in inpatient departments listed in order of higher rates of use included ampicillin (amoxicillin), metronidazole, cloxacillin, co-trimoxazole, gentamicin, penicillin, cefotaxime, erythromycin, chloramphenicol, ciprofloxacin, nitrofurantoin, doxycycline and ceftriaxone and tetracycline. Amikacin and nalidixic acid were rarely prescribed. The following are demonstrated patterns in which the following are cited as characteristic.
  - Prescribing antibiotics in clinical conditions for which use of antibiotics are considered not justified due to prescribers' failure to carry out precise diagnosis of presenting clinical cases and sufficiently establishing need for antibiotic use in their treatment before decisions to prescribe antibiotics are taken. The pattern is more prevalent in Government than CHAL hospitals and among individual hospitals is mostly seen at Queen II Hospital where the drugs for this reason are seen to be most frequently misused.
  - Prescribing certain antibiotics, notably ampicillin, penicillin, co-trimoxazole, metronidazole and gentamicin, for all types of infections but with dominance of their prescribing in particular infections.

- Prescribing certain antibiotics, for example cloxacillin, erythromycin, third generation cephalosporins (TGCs), ciprofloxacin and nitrofurantoin predominantly for particular infections only.
- Rare prescribing of amikacin and nalidixic acid though available as formulary antibiotics.
- Ampicillin is shown as the most frequently prescribed antibiotic in all types of infections except in gastrointestinal and bone infections where metronidazole is documented as the most frequently prescribed antibiotic. Individual infection types are treated most commonly with indicated antibiotics listed in order of their prescribing dominance as shown below.
  - Ampicillin, Co-trimoxazole, Penicillin, Gentamicin or Metronidazole for *respiratory tract infections.*
  - Ampicillin, Cloxacillin, Metronidazole and Gentamicin for *skin and soft tissue infections.*
  - Metronidazole, Co-trimoxazole, and Ampicillin and Cefotaxime for *gastrointestinal infections.*
  - Ampicillin, Metronidazole, and Gentamicin or Ciprofloxacin for *genitourinary tract infections.*
  - Ampicillin, Penicillin, Chloramphenicol and Metronidazole for central nervous system infections (meningitis).
  - Metronidazole, Ampicillin and Gentamicin for *bone infections (Osteomyelitis).*
  - Ampicillin, Gentamicin and Metronidazole for septicaemia.
  - Ampicillin, Co-trimoxazole of pyrexia of unknown origin.
- Antibiotic selection for prescribing in given cases of infections appeared to be largely based on the characteristic literature documented intrinsic activities of selected antibiotics against infecting pathogens of suspect rather than on local antibiotic sensitivity patterns of such pathogens. This mode of antibiotic prescribing is both liable to treatment failures and over-prescription of antibiotics.

5.1.5 Predictions of effectiveness of antibiotic treatment in inpatient department of study sites [Section 4.1.1.4] [Objective 1.3.1.2(vi)]

From calculated percentage overall activities of commonly prescribed antibiotics against most commonly associated pathogens with prescriber diagnosed

infections or by considerations of literature obtained antibiotic resistance patterns of bacterial pathogens associated with these infections the following can be inferred:

- With the exception of respiratory tract and also central nervous system infections where ampicillin exhibited appreciably high percentage overall activities (POAs) against locally determined pathogens associated with these infections, the use of ampicillin is predicted to be ineffective in treating established leading infections at study site hospitals. This includes the predominant use of the antibiotic in treating the rarer infections namely, osteomyelitis, bacteraemia and pyrexia of unknown origin.
- On the basis of calculated POAs [Appendixes 12(iv) and 12(v)], the use of co-trimoxazole, though observed to be the second most frequently prescribed antibiotic in treating respiratory and gastrointestinal tract infections, is predicted to be highly ineffective in treating infections of the respiratory and gastrointestinal tract. Gram-negative bacilli, the most implicated pathogens in gastroenteritis for which the antibiotic is most prescribed, are by local pathogen sensitivity patterns highly resistant to the co-trimoxazole (Table 4.2.5).
- Ciprofloxacin, third generation cephalosporins (TGCs) and chloramphenicol showed relatively high POAs against bacterial pathogens commonly associated respectively with *respiratory tract, skin and soft tissue* and *genitourinary tract infections* and are predicted to give favourably high response rates when used empirically in treating these infections. Ciprofloxacin may not be used for first line empiric therapy for respiratory and skin and soft tissue infections because of the dominant association of gram-positive cocci with these infections and the literature documented moderate activity of the antibiotic against these bacterial pathogens.

5.1.6 Antibiotic prescribing in post-surgical-wound treatment [Section 4.1.1.5] [Objectives 1.3.2.1 (vi)]

- Antibiotic prescribing for the prevention of surgical wound infections is done post-surgically at all study sites in contravention with literature recommended principles of antibiotic prescribing which required that prescribed antibiotics be given 1 to 2 hours before surgical incisions are made and discontinued 24 hours

after wound closure or following one or two doses post-operatively (Bratzler & Houck, 2005:397, Osmon, 2000:105).

- The observed pattern of antibiotic prescribing for post-surgical wound prophylaxis is one in which the following antibiotics are mainly prescribed for the indicated surgical wound types:
  - Ampicillin and metronidazole prescribed in combination for abdominal surgical wounds.
  - Cloxacillin and ampicillin prescribed singly or in combination for non-abdominal surgical wound infections.
  - Ampicillin and metronidazole or ampicillin and gentamicin for caesarean surgical wounds.
- Patterns of antibiotic prescribing in post-surgical wound treatment as established predict episodes of failures in patients' responses to the prophylactic treatment of their surgical wounds and depict prescribers' lack of adequate knowledge in the bacteriology of surgical wound infections and the selection of antibiotics in the prophylaxis of such infections.
- A hundred per cent (100%) response rate of patients to post-operative prophylactic treatment of all surgical wound types was reported during periods of hospitalisation in spite of predictions of treatment failures based on antibiotic sensitivity patterns of common bacterial pathogens associated with post-surgical infections of the specified surgical wound types. This, however, is not necessarily seen as indicative of a hundred per cent effectiveness of prescribed antibiotics in preventing post-surgical wound infection development taking into consideration the high possibility of post-surgical wound infections clinically manifesting after patients have been discharged from hospital (Eriksen *et al.*, 2003: 15 & 16) principally due to the short periods patients stay in hospital after surgery.

5.2 Inferences on assessment of outpatient prescriptions (Section 4.1.2.1)

The following are inferred as conclusions drawn from demonstrated patterns of antibiotic prescribing in outpatient departments of study site hospitals.

5.2.1 Prescriber qualifications involved in prescribing antibiotics appropriately in outpatient departments [Objective 1.3.1.2(vii)]

- Principal prescriber qualifications involved in prescribing antibiotics in outpatient departments of primary and tertiary public health institutions in Lesotho are doctors and nurse clinicians with doctors in the majority (80%).

5.2.2 Patterns and the extent of appropriate prescribing of antibiotics in outpatient departments of study sites [Objective 1.3.1.2(i)]

A majority of prescriptions are written appropriately according to principles of antibiotic prescribing but mainly for cases with possible bacterial aetiologies.

- Prescribers at Scott hospital showed a tendency of not writing antibiotic prescriptions inappropriately for both treatment of infections or for cases where antibiotic uses were deemed unjustified.
- From interpretations of observed relatively high rates of appropriately written antibiotic prescriptions and rates of diagnosis of infections it is established that
  - prescribers in outpatient departments of study sites most of the time prescribe antibiotics appropriately for absolute bacterial infections in cases of *skin and soft tissue* and *genitourinary tract infections* and for possible bacterial infections in *respiratory tract infections*; and
  - prescribers at Motebang and Scott hospitals, displayed more competence in distinguishing respiratory tract infections with bacterial aetiologies from those of viral origins than their counterparts at other study hospitals.

5.2.3 Comparative abilities of prescriber classification groups in writing prescriptions of defined prescription categories in outpatient departments [Objective 1.3.1.2(vii)]

- Nurse clinicians prescribe antibiotics appropriately based on principles of antibiotic prescribing for cases of possible rather than absolute bacterial aetiologies. This most probably is due to reasons of restrictions in their terms of operational duties which limit them to prescribing antibiotics for infections at the primary health care level for less serious infections happening to be infections with possible rather than absolute bacterial aetiologies.
- Doctors in the alternative and in comparison prescribe antibiotics appropriately based on principles of antibiotic prescribing more often in cases of absolute than

possible bacterial aetiologies. With a high percentage of prescription categories A2 prescribed by doctors at some study sites, however, it can again be concluded that a high proportion of this qualification group would lack the expertise of differentiating bacterial infections of the respiratory tract from viral infections.

- Both doctors and nurse clinicians prescribe antibiotics inappropriately according to principles of appropriate antibiotic prescribing in the treatment of infections in outpatient departments at the same percentage frequency of 19.0%.

5.2.4 The impact of appropriateness of antibiotic prescribing on mean costs of antibiotic prescriptions in outpatient departments [Section 4.1.2.2] [Objective 1.3.1.2(ii)]

From observed average cost patterns of antibiotic prescriptions constituting different antibiotic prescription categories with defined degrees of appropriateness the following are concluded with regard to the impact of appropriateness of antibiotic prescribing on mean costs of antibiotic prescriptions in outpatient departments.

- Degrees to which antibiotic prescriptions are written appropriately according to principles of appropriate antibiotic prescribing do not have any significant impact on costs of antibiotic treatment in outpatient departments.
- Costs of antibiotic treatment in outpatient departments have been seen to be reflective rather of cases of infections for which antibiotics are prescribed than for the appropriateness of which antibiotic prescriptions are written according to principles of antibiotic prescribing.

5.2.5 Antibiotic wastage resulting from prescribing for unjustified clinical reasons [Objective 1.3.1.2(iii)]

- A significant 12% of the total cost of antibiotics prescribed for treatment in inpatient departments have the likelihood to be wasted on account of prescribed antibiotics being given for clinical conditions for which the use of antibiotics is not justified. This works out to be a significant amount within the Lesotho context and warrants the problem of inappropriate prescription of antibiotics for unjustified clinical conditions to be seriously addressed.

5.2.6 The extent and effectiveness predictions of single antibiotic prescribing in treating infections in outpatient departments [Section 4.1.2.3] [Objective 1.3.1.2(iv)]

- Antibiotics are prescribed singly mostly in treating infections of respiratory tract, skin and soft tissue and gastrointestinal tract infections in outpatient departments. Multiple antibiotic prescribing on the contrary is presumably seen mostly in cases of genitourinary tract infections complicated with vaginal or penile discharges, considering that prescribers treat genitourinary tract infections of the indicated description using multiple antibiotics recommended in the Lesotho treatment guidelines to cover different categories of causative agents likely to be implicated in the infection type (Ministry of Health & Social Welfare, 2006: 64-67).
- By considerations of bacterial pathogen associations with infections commonly diagnosed in outpatient departments and the sensitivity patterns of bacterial pathogens to prescribed antibiotics, the following are inferred with respect to expected effectiveness of single prescribed antibiotics in treating infections in outpatient departments:
  - Single prescriptions of **ampicillin, erythromycin, penicillin and doxycycline or tetracycline,** are predicted to be generally ineffective in treating respiratory tract, skin and soft tissue and gastrointestinal and genitourinary tract infections in outpatient departments on the basis of their activity patterns against common pathogens associated with the infections. Exceptions take place in cases where *Streptococcus pyogenes and Streptococcus pneumoniae* are sole causative agents (Tables 4.2.3 and 4.2.4).
  - Based on its activity patterns against gram-positive and gram-negative bacterial pathogens, single prescriptions of **co-trimoxazole** are predicted to be highly ineffective against all infection types seen and treated in outpatient departments (Tables 4.23, 4.24 & 4.25).
  - Single prescriptions of **cloxacillin** are predicted to be significantly effective in treating *Staphylococcus aureus* and *S. pyogenes* infections of the skin but less so in treating same infections should *Staphylococcus epidermidis* and *S. pneumoniae* be the implicating pathogens (Table 4.2.4)

- Single prescriptions of combined formulations of **ampicillin and cloxacillin** are predicted to have higher positive treatment outcomes when used in treating respiratory tract and skin and soft tissue infections than either antibiotic alone on the basis of ampicillin exhibiting higher activities than cloxacillin against streptococci and cloxacillin similarly exhibiting higher activities than ampicillin against staphylococci (Table 4.2.4).
- Single prescriptions of ciprofloxacin are predicted to have the best treatment outcomes among all available antibiotics used routinely in treating infections among outpatients in spite of literature documented evidence of limited or moderate activity of the antibiotic against gram-positive cocci (British Medical Association & Royal Pharmaceutical Society of Great Britain, 2002:294).

5.2.7 The impact of antibiotic stock unavailability on prescribers' choice of antibiotics in outpatient departments [Section 4.1.2.3] [Objective 1.3.1.2(viii)]

- As a factor deemed to negatively limit prescriber's abilities to select antibiotics, antibiotic stock unavailability does not significantly influence the ability of prescribers to select antibiotics which in their opinion are most appropriate in treating diagnosed infections.
- Prescribers' ability to select antibiotics largely define characteristic patterns of antibiotic prescribing established by this study. For reasons of this ability of prescribers not seen as being influenced by antibiotic stock outs during the period of the study, patterns of antibiotic prescribing as established for outpatient departments are considered true patterns of antibiotic prescribing characteristic to prescribers of the drugs in Lesotho.

5.2.8 The extent to which prescribers establish patients' need for antibiotics before prescribing the drugs [Section 4.1.2.4] [Objective 1.3.1.2(ix)]

- Prescribers characteristically prescribe antibiotics for outpatients based solely on their clinical judgements from symptomatic assessment of patients.
- Prescribers in instances where signs and symptoms are suggestive of bacterial or viral infections or of non-infectious clinical conditions are unable to distinguish bacterial infections from conditions with other aetiological agents, indicating

prescribers' general lack of expertise in differential diagnosis to establish absolute bacterial infections.

5.2.9 Accuracy evaluations of prescriber diagnosed infections and its effects on appropriateness of antibiotic prescribing in outpatient departments [Section 4.1.2.5] [Objective 1.3.1.2(x)]

- Prescribers most often use diagnostic terms or describe symptoms non-indicative of any particular diagnosis with defined causative agents, showing lack of accuracy on their part in diagnosing and appropriately treating infections (Tables 4.1.28, 4.1.29, 4.1.30 and 4.1.31). This is predicted to create a characteristic pattern of antibiotic prescribing in which antibiotics would largely be seen to be prescribed in outpatient departments for non-bacterial infections and hence for the "wrong reasons".
- The majority of cases in which antibiotics were prescribed for the "wrong reasons" were seen in the treatment of respiratory tract infections.

5.2.10 Leading infections and their patterns of prevalence at study site outpatient departments [Section 4.1.2.5] [Objective 1.3.1.2(v)]

- *Respiratory tract infections* constitute more than half of all cases of infections seen and treated at outpatient departments of study sites and related infection is thus noted as the leading infection for which antibiotics are prescribed among outpatients. It is followed in that order by *skin and soft tissue, genitourinary tract* and *gastrointestinal and mouth infections*.
- No "outbreaks" of any infection occurred during the course of the study and patterns of antibiotic prescribing as the study established are considered reflective of what generally prevails at study sites without any influences of unprecedented increases in rates of diagnosis of infection types on results of the study.

5.2.11 Patterns of antibiotic prescribing in the treatment of diagnosed infections in outpatient departments [Section 4.1.2.5] [Objective 1.3.1.2(vi)]

- The most commonly prescribed antibiotics in outpatient departments for infection types most often diagnosed include:

- ampicillin, co-trimoxazole, erythromycin, and penicillin, for r*espiratory tract infections*;
- Erythromycin, ciprofloxacin, metronidazole, ampicillin, doxycycline/ tetracycline, co-trimoxazole for *genitourinary tract infections;*
- Cloxacillin, ampicillin, penicillin, erythromycin and co-trimoxazole for s*kin and soft tissue infections;*
- Penicillin, metronidazole, ampicillin, co-trimoxazole and erythromycin for gastrointestinal tract and mouth infections.

5.2.12 Pathogen associations with and effectiveness predictions of prescribers' choices of antibiotics in the treatment of diagnosed infections [Section 4.1.2.5] [Objective 1.3.1.2(vi)]

Inferences on bacterial pathogens' associations with various diagnosed infections (Table 4.2.3) at study sites and predictions of effectiveness of commonly prescribed antibiotics used in their treatment as inferred from results of pathogen antibiotic sensitivity data [Table 4.2.4 and 4.2.5 and percentage overall activity (POA) determinations of antibiotics (Appendices 12(iv), 12(vi) 12(ix), 12(xiii) and 12(xiv)] are as outlined below.

- **Respiratory tract infections**

° Pathogens associated with respiratory tract infections among the study population as results have shown include the following:
  - Lower respiratory tract infections: *S. pneumoniae*, *S. pyogenes*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, (gram-positive cocci); *Klebsiella, Haemophillus influenzae,* (gram-negative bacilli).
  - Throat infections: *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and non-haemolytic streptococci, as well as the gram-negative bacilli, *Klebsiella*, *Proteus* spp and *Haemophilus influenza*

° Ampicillin and co-trimoxazole demonstrated low percentage overall activities (POAs) against common isolates of respiratory tract infections and are predicted to have generally low treatment outcomes when used in treating bacterial infections of the respiratory tract particularly in elderly patients, patients with bronchiectasis, patients with previous hospital admission or

previous history of corticosteroids who are considered at risk of respiratory tract infections with GNB.

- Ampicillin showed greater percentage activities (PAs) against pathogens associated with throat infections in comparison with penicillin and erythromycin and is indicated as preferable to the latter antibiotics in treating bacterial pharyngitis.
- Ciprofloxacin, TGCs, cloxacillin and chloramphenicol from their determined POAs are preferable in that order to ampicillin and co-trimoxazole in the empiric treatment of respiratory tract infections.

- **Genitourinary tract infections**

- Pathogens associated with urinary tract infections (UTI) among the Basotho population including pathogens considered to be opportunistic but now appearing as emerging regular pathogens associated with the infection among the population group probably due to HIV/AIDS associated decreased immune competency of the population include the following:
  - For UTI: *Escherichia coli, Klebsiella*, *Proteus*, *Pseudomonas* spp) enterococci, *Staphylococcus saprophyticus* and *Streptococcus pyogenes* (gram-positive cocci) (Table 4.2.3, Ohl & Pollack, 2005:893, Ministry of Health & Social Welfare, Lesotho, 2004: 233).
  - For concurrently diagnosed UTI and penile or vaginal discharges: *Escherichia coli Klebsiella*, *Proteus*, *Pseudomonas* spp, enterococci (non-haemolytic streptococci) and *Streptococci pyogenes*. (*Staphylococcus aureus* and *Staphylococcus epidermidis*), *Neisseria gonorrhoea* and *Chlamydia trachomatis* (Table 4.2.3).
- Ampicillin and co-trimoxazole do not have much benefit in the treatment of UTIs on the basis of their high resistance rates to gram-negative bacilli and percentage overall activities against pathogens implicated against UTI [Table 4.2.5; Appendixes 12(xii,xiii and xiv)].
- Nalidixic acid has higher chances than nitrofurantoin in the successful empiric treatment of UTIs with *Pseudomonas, Klebsiella* and *Proteus* as aetiological agents in mixed infections of the tract. Nitrofurantoin demonstrates higher PA against *Escherichia coli,* the dominant causative agent of UTI, than nalidixic

acid. The latter antibiotic for this reason is suggested for a second choice prescription in the event of treatment failures with nitrofurantoin which again for reasons given above is suggested for first choice prescriptions in UTIs (Table 4.2.5).

- Specimens for UTI complicated with urethral and vaginal discharges showed strong presence of *Staphylococcus aureus* (Figures 4.2.15 and 4.2.16). The organisms are speculated despite their dominant presence in these specimens to be contaminants, based on the non-associations of the pathogens with urinary tract infections (Holmes, 2005:768) and admissions of staff of Queen II microbiology laboratory that *S. aureus* are almost always isolated from urethral and vaginal swab specimens. Until further investigations showed these pathogens as associated pathogens with urethritis or cervicitis among the population, antibiotic treatment of the infections may not be given to target *S. aureus* as causative agents.
- Ciprofloxacin and TGCs have the best chances of successfully treating UTIs with or without concurrent diagnosis of urethral or vaginal discharges in view of their activities against associated pathogens of the infections (Table 4.2.3 and 4.2.5; Appendices xix &xiv). With the exception of cases where there are reasons to exclude the implication of other pathogens apart from *N. gonorrhoea* and *C trachomatis* as aetiological agents of diagnosed urethritis or cervicitis literature recommended dosage regimens of 7 - 14 days courses of treatment using the antibiotics in treating the infection are suggested (Stamm , 2005: 1719).

- **Skin and soft tissue infections**

- The most reportedly seen and treated skin and soft tissue infections in outpatient departments include abscesses, cellulitis, impetigo, lacerations and bruises, septic ulcers and lesions, skin rashes and animal bites (Table 4.1.32); which by literature findings and with the exception of animal bites are considered to be associated with staphylococci, (*Staphylococcus aureus* and *Staphylococcus epidermidis* mainly), and streptococci, particularly *Streptococcus pyogenes* (Musher, 2005: 826).
- When prescribed as a single antibiotic cloxacillin, among antibiotics most commonly prescribed in the treatment of skin and soft tissue infections, is the

most effective for the empiric treatment of commonly diagnosed skin and soft tissue infections in outpatient departments by results of culture sensitivity tests of gram-positive cocci organisms against available antibiotics (Table 4.2.4).

- Combined prescription of cloxacillin and ampicillin is predicted to have better treatment outcomes than either antibiotic alone in treating skin and soft tissue infections in which gram-positive cocci other than *Staphylococcus aureus* and *Streptococcus pyogenes* are implicated as causative agents (Table 4.2.4).
- Penicillin, erythromycin, co-trimoxazole and tetracycline are predicted to be largely ineffective in the empiric treatment of commonly seen and treated skin and soft tissue infections in outpatient departments.

- **Gastrointestinal/mouth infections**

- Dental and mouth infections, gastroenteritis, gastritis, abdominal pain and perianal sores are the most reportedly seen and treated infections of the gastrointestinal tract in outpatient departments (Table 4.1.33). From literature findings and in absence of data on local pathogens associated with gastrointestinal and mouth infections, these are considered associated with anaerobic bacteria including *Prevotella spp*, *Porphyromonas spp* and *Fusobacterium* spp *Bacteroides, Porphyromonas, Peptostreptococcus* and enteric *Salmonella*, *Shigella dysenteriae*, *Yersinia enterocolitica* and GNB, principally *Escherichia coli* and *Klebsiella*, as their causative pathogens (Kasper, 2005:941).
- Frequencies of antibiotic prescribing for and diagnoses of gastrointestinal infections among outpatients (Tables 4.1.30 & 4.1.33) showed a pattern in which ampicillin and metronidazole, were observed to be prescribed together probably for infections assumed to be caused by GNB and anaerobic organisms of the gastrointestinal tract, penicillin in mono-therapy mostly for dental and mouth infections with which gram-positive cocci anaerobic infections are associated and co-trimoxazole mainly for gastroenteritis and dysentery with which *Escherichia coli and Shigella* spp are associated (Russo, 2005:879 & 882; Keusch & Kopecko, 2005:904).
- Co-trimoxazole and ampicillin by their local activity patterns are highly inactive against GNB and are predicted to be ineffective in treating mixed infections of

anaerobic bacteria and *E. coli* or infections in which *E. coli* is the sole causative pathogens. (Table 4.2.4).

- Ciprofloxacin prescribed alone and in combination with metronidazole on the basis of local pathogen antibiotic sensitivity patterns and literature recommendations are recommended in treating infectious diarrhoea or bacterial dysentery and anorectal sores (Butterton & Calderwood, 2005:759; Keusch & Kopecko, 2005:905).
- Penicillin or ampicillin or amoxycillin/clavulanic acid are recommended in single antibiotic therapy of dental and mouth infections (Kasper, 2005: 945).

♦ **Sources of possible antibiotic misuse in outpatient departments**

- Lack of prudent diagnostic workup to establish presence of bacterial infections and hence needs of antibiotic use particularly in respiratory tract infections before antibiotics are prescribed has been established as a major source of antibiotic misuse and overuse in outpatient departments.
- Antibiotics most misused or over prescribed for the "wrong reasons" include in order of their relative frequencies of prescribing for these reasons ampicillin, co-trimoxazole, penicillin and erythromycin. These antibiotics predictably demonstrate low activities against pathogens they are intrinsically known to be active most probably for reasons of their misuse or overuse. These are factors that are known to contribute to pathogen antibiotic resistance development (World Health Organisation, 2001:1).

5.3 Inferences on bacterial pathogen sensitivity data analysis

5.3.1 Bacterial pathogens and the extent of their isolations at study sites [Section 4.2.1] [Objective 1.3.1.2(xi)].

- Major pathogens isolated from all study site hospitals included *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pyogenes, Streptococcus pneumoniae, non-haemolytic streptococci* (gram-positive cocci); *Escherichia coli, Klebsiella* spp, *Proteus* spp (enteric gram-negative bacilli), *Pseudomonas* spp, *Acinebacter* spp, *Haemophillus influenzae, Haemophilus parainfluenza* [gram-negative bacilli (GNB)]; and *Neisseria* spp (gram-negative cocci).

- Rarer pathogens isolated included *Corynebacterium spp* (gram-positive bacilli) *Shigella* spp, *Salmonella* spp, and *Peptococcus* spp and *Bacteroides* spp (anaerobic bacteria). Their isolations were done mainly at the Queen II hospital.

5.3.2 Bacterial pathogen associations with diagnosed infections [Section 4.2.2] [Objective 1.3.1.2(xii)]

- All infections commonly diagnosed at study sites are generally associated with gram-positive cocci and gram-negative bacilli as aetiological agents with the exception of
  - eye infections which are associated with gram-positive cocci only,
  - meningitis with which anaerobic bacteria and gram-negative cocci *Neisseria* spp are additionally associated as aetiological agents,
  - wound infections and vaginal discharges with which anaerobic bacteria are additionally associated as aetiological agents and
  - gastrointestinal infections for which specimens were observed not to be sent routinely to laboratories for culture sensitivity testing.
- *Staphylococci* (*Staphylococcus aureus* mainly or *Staphylococcus epidermidis*) among gram-positive cocci are observed major pathogens associated with most infections including lower respiratory tract infections with or without parapneumonic pleural effusions, ear infections, eye infections, throat infections, wound infections and bacteraemia.
- Urethritis (penile discharges) and cervicitis (mucopurulent vaginal discharges) showed dominant associations with *Staphylococcus aureus.* However, until further studies prove the organisms as aetiological agents of urethritis and cervicitis, the strong presence of *Staphylococcus aureus* in penile and vaginal discharges can be taken as a case of specimen contamination that does not have to be treated.
- *Streptococcus pneumoniae* showed strong associations with lower respiratory tract infections with or without parapneumonic pleural effusions, meningitis, throat infections, eye infections and bacteraemia.
- With a show of dominance in throat infections non-haemolytic streptococci, including enterococci (*Enterococcus faecium* and *Enterococcus faecalis*) which

are known opportunistic infections causing infections in debilitated and immunocompromised patients, have been observed as emerging major causative agents for many infections including, apart from throat infections, lower respiratory tract infections with or without parapneumonic pleural effusions, eye infections, bacteraemia and cervicitis.

- Enteric GNB, particularly *Escherichia coli* and also *Klebsiella* and *Proteus* spp or the environmental GNB, *Pseudomonas* spp, are major causative agents of lower respiratory tract infections with parapneumonic pleural effusions. *Klebsiella* spp among the gram-negative bacilli are the pathogens most frequently associated with lower respiratory tract infections without parapneumonic pleural effusions (Figure 4.1.13). The pathogens particularly *Escherichia coli*, are also strongly associated with uncomplicated urinary tract infections. They are important causative agents of ear infections where *Proteus* and *Pseudomonas* showed dominance, wound infections, and bacteraemia.
- Gram-negative bacilli (*Escherichia coli*, *Klebsiella* and *Pseudomonas* spp) were seen to be associated with urethritis and cervicitis. In the absence of non-associations of the pathogens with these infections (Holmes, 2005:765) the presence of GNB in specimens of penile and vaginal discharges indicate concurrent UTI with urethritis and cervicitis. Empiric antibiotic prescribing in urethritis and cervicitis should also take into consideration possible concurrent presence of urinary tract infections particularly if symptoms of UTI exist.
- Anaerobic bacteria involvement in infections is seen mainly in meningitis where *Bacteroides* spp were seen as implicating pathogens and also wound infections and cervicitis where *Peptococcus* spp were isolated.

5.3.3 Summary conclusions on diagnosed infections and associated pathogens for coverage in empiric antibiotic treatment [Section 4.2.2;Table 4.2.3] [Objective 1.3.1.2(xii)]

Locally associated pathogens with commonly diagnosed infections at study sites are outlined as indicated below with the most dominant pathogen in each case of the specified infections listed first.

- **Ascites complicated with bacterial peritonitis**: Gram-negative bacilli, particularly *Escherichia coli* and *Klebsiella* spp and gram-positive cocci principally Staphylococci (*Staphylococcus aureus* and *Staphylococcus epidermidis*) and *Streptococcus pneumoniae*.

- **Bacterial meningitis**: Gram-positive cocci: *Streptococcus pneumoniae, Staphylococcus epidermidis* and *Staphylococcus aureus* and non-haemolytic streptococci; gram-negative bacilli: *Haemophilus influenzae* and *Escherichia coli, Klebsiella* spp and *Pseudomonas* spp (Associated mainly with meningitis with diabetes, cirrhosis, alcoholism or chronic urinary tract infections (Ohl & Pollack, 2005:890-893); gram-negative cocci: *Neisseria meningitidis.* Anaerobic bacteria*: Bacteroides spp.* In the event of bacterial meningitis being caused by haematologic seeding of pathogens from an existing infection, knowledge of possible organisms associated with the existing infection will provide a clue to the probable causative agents of the meningitis.

- **Lower respiratory tract infections with or without parapneumonic effusions:**

- Gram-positive cocci: *Staphylococcus aureus, Streptococcus pneumoniae, Staphylococcus epidermidis*, *Streptococcus pyogenes,* non-haemolytic streptococci; gram-negative bacilli: *Haemophilus influenzae*, *Escherichia coli, Klebsiella spp*).

- **Ear infections:** Gram-positive cocci: *Staphylococcus aureus*, *Streptococcus pneumoniae*, non-haemolytic streptococci, *Staphylococcus epidermidis*; Gram-negative bacilli: *Proteus* spp, *Pseudomonas, Klebsiella and Escherichia coli.*

- **Throat infections:** Gram-positive cocci: Non-haemolytic streptococci, *Streptococcus pyogenes, Streptococcus pneumoniae,* and *Staphylococcus aureus*; Gram-negative bacilli; *Klebsiella, Proteus, Pseudomonas* spp.

- **Eye infections:** Gram-positive cocci: *Staphylococcus epidermidis Staphylococcus aureus, Streptococcus pneumoniae*, *Streptococcus pyogenes*, non-haemolytic streptococci.

- **Wound infections:** Gram-positive cocci: *Staphylococcus aureus Staphylococcus epidermidis, Streptococcus pyogenes*, non-haemolytic streptococci, *Streptococcus pneumoniae*; Gram-negative bacilii: *E. coli, Proteus, Pseudomonas* and *Klebsiella.*

- **Bacteraemia/Septicaemia:** Gram-positive cocci: *Staphylococcus aureus, Staphylococcus epidermidis*, *Streptococcus pneumoniae,* and non-haemolytic streptococci; gram-negative bacilli: *Escherichia coli, Klebsiella* spp and *Pseudomonas* spp. Infections from which haematologic seeding of pathogens occurred normally provide means of accurately guessing probable afflicting pathogens.

- **Urinary tract infections:** Gram-negative bacilli: *E. coli. Klebsiella* spp. *Proteus* spp and *Pseudomonas;* Gram-positive cocci: *Staphylococcus aureus* and non-haemolytic streptococci (enterococci) *Staphylococcus saprophyticus.*

- **Urethritis (Penile discharges):** Gram-negative bacilli: *Escherichia coli, Klebsiella* spp, *Pseudomonas* spp.; Gram-positive bacilli: *Corynebacterium* spp Gram-positive cocci: *Staphyloccocus epidermidis, Streptococcus pneumoniae. (Staphylococcus aureus* present as a contaminant).

- **Cervicitis (mucopurulent vaginal discharges):** Gram-negative bacilli: *Escherichia coli*, *Klebsiella* spp *Proteus* spp, *Pseudomonas* and *Salmonella*; Anaerobic bacteria: *Peptococcus*. Gram-positive cocci: *Streptococcus pyogenes* and non-haemolytic streptococci (enterococci), *Streptococcus pneumoniae (Staphylococcus aureus* present as a contaminant).

5.3.4 Patterns of bacterial pathogen sensitivities to formulary antibiotics [Sections 4.2.3] [Objective 1.3.1.2(xiii)]

Gram-positive cocci

- Rates of resistance of *Streptococcus pneumoniae* to β-lactam and other antibiotics determined as 23% for penicillin and erythromycin and 28% for

tetracycline compares favourably with resistance rates of 24.6% and 25% similarly reported for the pathogen against same antibiotics in that order by the year 2000 in global study reports. The agreement of these results with those of the global studies, confirms the conclusion from those studies which reported a global increase in resistance rates of *Streptococcus pneumoniae* to β-lactam and other antibiotics.

- Highly penicillin resistant strains of *Streptococcus pneumoniae* were observed to abound at study site hospitals and negate the empiric prescription of third generation cephalosporins (TGCs) in treating pneumococcal infections.
- *Streptococcus pyogenes* has developed resistance of as high as 39.5% against penicillin and erythromycin. The antibiotics for this reason may no longer be used as first-line antibiotic treatment of *S. pyogenes* infections in Lesotho in accordance with literature recommendations (Table 4.2.4, Wessels, 2005:825-826).
- On the basis of observed relatively high resistance rates of streptococci (*Streptococcus pneumoniae, Streptococcus pyogenes* and non-haemolytic streptococci) against co-trimoxazole, the predominant prescription of co-trimoxazole in treating respiratory tract infections and other streptococcal infections among outpatients is predicted to have high treatment failures (Table 4.2.4). The empiric treatment of these infections with the antibiotic may have to be avoided.
- Penicillin sensitive and methicillin susceptible strains of *Staphylococcus aureus* represent about 70% [i.e. the sensitivity rate of the pathogen to methicillin/cloxacillin (Table 4.2.4)]. This gives a 30% proportion of all isolates of *Staphylococcus aureus* in hospitals in Lesotho being methicillin resistant. This is lower than an expected 40% - 50% of isolates being methicillin resistant strains according to Lowy (2005:821).
- Cloxacillin, currently prescribed as the major antibiotic in the treatment of skin and soft tissue infections has good prospects of being used successfully in treating *Staphylococcus aureus* infections and, on the basis of the pathogens resistant to it being equally resistant to other antibiotics, is not to be substituted empirically with any of the antibiotics in current use (Jones *et al.,* 2003:408).
- Vancomycin, on the basis of literature findings reporting its 100% activity against methicillin resistant strains of *S. aureus* (Brown & Ngeno, 2007:223) is

recommended for use as a second choice antibiotic in the treatment of staphylococci infections unresponsive to cloxacillin.

Gram-negative bacilli (GNB)

- All major gram-negative bacilli isolates, namely, *Escherichia coli, Klebsiella, Proteus* and *Pseudomonas spp* are highly resistant to ampicillin, tetracycline, chloramphenicol and co-trimoxazole. The antibiotics may not be used in the empiric treatment of infections in which GNB are implicated as sole causative pathogens (Table 4.2.5).
- GNB generally are sensitive in the range of 71.1% to 94.0% to ciprofloxacin, gentamicin, amikacin and TGCs with the exceptions of *Klebsiella* which is 49% sensitive to TGCs and *Proteus* spp which is 36% sensitive to amikacin.
- The observed high resistances of *Escherichia coli* and other GNB to ciprofloxacin is probably attributable to both the low dosing and extensive use of the antibiotic in treating urethritis or cervicitis complicated with urinary tract infections in which the pathogens are implicated. Diagnostic workups in clinical presentations of urethritis or cervicitis are advocated to be meticulously done to exclude concurrent UTI before treatments of the infections with single 500mg doses of ciprofloxacin are effected. In the event of UTI being concurrently diagnosed with cervicitis or urethritis in such a diagnostic workup treatment should be 3 day or 7 -14 day courses of ciprofloxacin, depending on the severity of the urinary tract infection component of the infection, to adequately cover GNB.
- Third generation cephalosporin resistant strains of *Klebsiella* spp have been observed to exist in hospital environments in Lesotho. While the pathogens might have acquired this resistance through their acquisition of plasmid propagated extended spectrum β-lactamase genes in the environment (Russo, 2005:883), the possibility of indiscriminate use of the antibiotic in inpatient environments cannot be ruled out. A curtailment of the indiscriminate empiric prescribing of the TGCs (cefotaxime) is advocated in favour of the prescription of the antibiotic based on culture sensitivity results.
- High resistance rates of GNB towards co-trimoxazole as seen in the case of gram-positive cocci are also very probably attributable to an over-prescribing of

the antibiotic at study site hospitals. The rate of prescription of the antibacterial agent is recommended to be reduced or its prescribing suspended for a time period to reverse the clinical problems of resistance associated with the antibiotic at study site hospitals as currently established (Gould, 1999:460).

- Compared to their literature indicated activities against *Pseudomonas*, the aminoglycosides (gentamicin and amikacin), the quinolones (ciprofloxacin and nalidixic) and the TGCs (cefotaxime & ceftriaxone) were seen to currently exhibit good activity against *Pseudomonas* spp. (Table 4.2.5). To maintain their current levels of effectiveness against the pathogens a judicious use of the antibiotics by way of prescribers' adherence to principles of antibiotic selection and prescribing based on results of culture sensitivity tests is highly recommended.
- Based on the estimated 50% rate of resistance of *H. influenzae* against ampicillin as determined from the few isolates of the organism and which is much higher than the 25% indicated in the literature as the percentage of strains of *H. influenzae* which are β-lactamase producing and are resistant to ampicillin (Murphy, 2005:865; Elliot *et al.*, 2004:59), a high prevalence of β-lactamase producing strains of *H. influenzae* is speculated among the population of the study. The pathogen is also predicted to have high sensitivity rates against tetracycline, chloramphenicol, and gentamicin, on the basis of the relatively high sensitivities shown by same few isolates of the pathogen tested against the antibiotics (Table 4.2.5). Combinations of β-lactam/β-lactamase inhibitors e.g. amoxicillin/clavulanic acid also tetracycline, chloramphenicol, and gentamicin are suggested on the basis of the above for treating *H. influenzae* infections.

5.3.5 Variations in percentage yearly resistances of bacterial isolates to formulary antibiotics over a six-year period from January 2000 to December 2005 : [Section 4.2.3.2] [Objective 1.3.1.2(xiv)]

- Increasing resistances of streptococcal isolates principally *S. pyogenes* and *S. pneumoniae* to antibiotics they are known to be intrinsically susceptible to, including ampicillin, penicillin, and erythromycin have been established (Figures 4.2.17; 4.2.18; 4.2.19). Mechanisms of bacteria antibiotic resistance development by selective pressure due to extensive prescription of antibiotics in the population are postulated to be the means of the resistance development by

these organisms to the antibiotics on account of established high rates of use of the antibiotic (Colgan & Powers, (2001:999) (Tables 4.1.15 and 4.1.33).

- Methicillin resistant strains of *Staphylococcus aureus* are observed to be increasing in the population, though slowly. The observation underscores the need to introduce antibiotics that are effective against these strains of the pathogen into study sites antibiotic armoury for the treatment of staphylococci infections in the event of treatment failures with cloxacillin, the currently used semisynthetic penicilinase resistant antibiotic at study site hospitals (Table 4.2.9; Figure 4.2.20).

- Resistance trends of bacterial pathogens to antibiotics less used at study site hospitals, notably chloramphenicol, tetracycline, amikacin, ciprofloxacin, nitrofurantoin and nalidixic acid have generally been stable or decreasing (Figures 4.2.23; 4.2.21; 4.2.26; 4.2.27; 4.2.29).
- Resistance of *Streptococcus pneumoniae* to tetracycline increased over the six-year period of pathogen antibiotic sensitivity data study (Figures 4.2.21 & 4.2.18) parallel to increases observed for the pathogen to penicillin, confirming similar reports by other researchers (Inoue *et al*, 2004:47).
- Increase in yearly resistances or high stable such resistances of a number of organisms to antibiotics have been noticed most often in cases of antibiotics established by research findings as most frequently prescribed. These include,
  - increasing yearly resistance rates of *Streptococcus pyogenes* to ampicillin and penicillin;
  - increasing yearly resistance rates of *Staphylococcus aureus* to ampicillin and penicillin;
  - high stable yearly resistance rates of GNB (*Escherichia coli, Klebsiella, Proteus* and *Pseudomonas* species) to ampicillin;
  - increasing yearly resistance rates of *S. pneumoniae, S. pyogenes and Staphylococcus aureus* and *Escherichia coli* to erythromycin; and
  - increasing yearly resistance rates of *S. pyogenes*, S. *pneumoniae* and non-haemolytic streptococci *Staphylococcus aureus* and GNB (*Escherichia coli, Klebsiella, Proteus* and *Pseudomonas* species) to co-trimoxazole.

- Variations of yearly resistances of GNB (*Escherichia coli, Klebsiella, Proteus* and *Pseudomonas* species) to 3rd generation cephalosporins (TGCs) demonstrated as increases or decreases during discrete periods of the indicated culture sensitivity study period were seen to parallel variation trends in yearly resistances shown by *Staphylococcus aureus* to the antibiotic (Figure 4.2.24).

° Gram-negative bacilli (*Escherichia coli, Klebsiella, Proteus* and *Pseudomonas* species) and also *Staphylococcus aureus* demonstrated stable trends in their variations in yearly resistance rates to the aminoglycosides during indicated culture sensitivity study period, with amikacin showing higher stable levels of activity against the pathogens than gentamicin (Figure 4.2.25 and 4.2.26).

° *Enterococci faecium* and *Enterococci faecalis* (non-haemolytic streptococci) with their known intrinsic resistances to the aminoglycosides exhibited increasing trends in their percentage yearly resistance variations to gentamicin over the culture sensitivity study period most probably attributable to mechanisms of selective pressure due to over-prescribing of the antibiotic among inpatients (Figure 4.2.25).

5.3.6 Antibiotic selection for empiric treatment of infections [Section 4.2.4] [Objective 1.3.1.2(xv)]

° Characteristics of antibiotics with respect to the extent of their effective coverage of pathogens most possibly implicated in given infections or their successful therapeutic application in treating given infections as well as cost limitations disadvantaging their use in treating such infections, have been quantified by means of derived formulae and designated as antibiotics'

- percentage overall activity (POA);
- treatment success to failure ratio (ATFR); and
- antibiotic selection factor (ASF).

° Among antibiotics evaluated, **ciprofloxacin**, based on its POA or ATSFR values and taking into account its characteristic moderate activities against gram-positive cocci is considered for first-line prescribing in:

- Ascites complicated with primary or spontaneous bacterial peritonitis.

  - Meningitis (if haematologic seeding resulting in the infection does not come from sites of infections suggestive of gram-positive cocci involvement)
  - Ear infections.
- Based on its ASF values **ciprofloxacin** is again considered for first choice prescribing in above infections **except** meningitis for which **chloramphenicol** is considered first choice.
- Based on antibiotics' POA or ATFR values **cefotaxime** is selected for first-line prescribing in urinary tract infections uncomplicated with penile or vaginal discharges while based on ASF considerations **ciprofloxacin** would again be the antibiotic for first line prescribing.
- With the extent of their effectiveness taken into consideration, **ampicillin** and **co-trimoxazole** may not be considered for first-line empiric prescribing in infections commonly associated with gram-negative bacilli and staphylococci infections.
- The aminoglycosides, for reasons of their not being tested against all pathogens seen to be associated with infection, had been excluded from the antibiotic selection process because ATSFR or ASF values could not be determined for them.

5.4 Inferences on factors attributing to patterns of antibiotic prescribing

5.4.1 Percentage frequency of distribution of respondents according to their demographic data [Section 4.3.1.2[[Objective 1.3.1.2(xvi)(a)]

- Respondents to questionnaires constitute doctors and nurses in the specific qualification categories of physician specialists, surgical; consultants, general practitioners, nurse clinicians, registered nurses and nurse assistants.
- Doctors and nurse clinicians are the principal prescribers of antibiotics.
- Doctors practise mainly in urban health institutions while nurses, with the exception of few nurse clinicians practise in rural health centres.
- Nurses that did not receive formal training in the diagnosis and treatment of infections have been involved in antibiotic prescribing. The finding is inappropriate and indicated as a problem that needs attention by health policy makers in both Government and CHAL institutions.

- Long years of working experience do not necessarily improve prescribers' capabilities of prescribing antibiotics appropriately based on principles of rational antibiotic prescribing and shorter years of practising may not be considered as a factor that seriously compromises the appropriateness of antibiotics prescribed in treating infections.
- The majority of prescribers within study site HSAs see and treat on the average 63 and up to more than 100 patients a day, giving rise to a large prescribers' workload that is considered a factor compromising efficient diagnosis and treatment of infections.
- Capabilities of doctors to prescribe antibiotics appropriately for outpatients are affected much less by their workload or insufficient knowledge in principles of antibiotic prescribing as compared to limitations imposed by the same factors in their ability to prescribe for inpatients.

5.4.2 Availabilities and capacities of microbiology laboratories at respondents' practice sites [Section 4.3.1.2] [Objective 1.3.1.2(xvi)(b)]

- Microbiology laboratory facilities with functional capacities enough to provide information to doctors to aid in their appropriate diagnosis and treatment of infections are available at all study site hospitals.
- Inefficient operational systems manifesting as deficiencies in information flow between medical and laboratory staff contribute significantly to the non-use microbiology facilities by prescribers. This is identified as an important limitation to prescribers' use of microbiology laboratory-based data in making decisions in infection diagnosis and treatment.

5.4.3 Influence of patient and prescriber related factors on prescribers' decisions to prescribe antibiotics [Section 4.3.2] [Objective 1.3.1.2(xvi)(c)]

- **Patient-related factors**

- Nurse clinicians among the category of nurse prescribers are significantly and most influenced to prescribe antibiotics by patients' requests for or their expectations to be treated with antibiotics. Registered nurses and nursing assistants are not significantly influenced by the factor.

- Doctor prescribers generally and particularly physician specialists are not influenced to any significant the extent by patients' requests for or their expectations to be treated with antibiotics.
- In spite of the observed major influence of patients' requests for and their expectations to be treated with antibiotics on nurse clinicians to prescribe antibiotics, the low nurse clinician to doctor ratio [1:5 (8:39)] from estimates makes the factor rather an insignificant contributor to inappropriate prescribing of antibiotics among prescribers at study sites.

- **Prescriber-related factors**

The study established the following prescriber-related factors which, with the exception of prescribers' past experiences, have been observed to have a negative impact on appropriateness of antibiotic prescribing within the five sites of study of this research. They include:

- a non-consideration of biomedical factors relating to patients in some cases of antibiotic prescribing by both doctors and nurse clinicians and thought to be accountable for about 12.1% and 17.6% of outpatient and inpatient antibiotic prescriptions seen to be inappropriately written on the basis of prescribed antibiotics being given for clinical conditions that did not require the use of antibiotics;
- prescribers' desires to eliminate or prevent infections which was identified as a major factor contributing to inappropriate prescribing and is thought to be responsible for observed high percentages of 80.8% and 65.4% of inpatient and outpatient prescriptions analysed and found to be inappropriately prescribed; and
- prescribers' dependence on their past experiences to treat infections with antibiotics which, though claimed by the majority of respondents to influence their antibiotic prescribing capabilities, have not been evaluated to the extent that would enable conclusions to be drawn on its impact on appropriateness of antibiotic prescribing.

5.4.4 Antibiotic prescribing in outpatient departments on the basis of positive establishment of presence of infections [Section 4.3.3] [Objective 1.3.1.2(xvi)(d)]

- All qualification categories of respondents equally demonstrated high tendencies of prescribing antibiotics on the basis of their suspicions of the presence of infections. From among all the qualification groups, the physician specialists appeared to be most regularly prescribing antibiotics on the basis of their suspicion of infections.
- Antibiotic prescriptions in outpatient departments were mostly inappropriately written for suspected cases of infections. This is an observed pattern of antibiotic prescribing seen to be largely dependent or directly accounted for by antibiotic prescribing behaviours of prescribers in outpatient departments.

5.4.5 The extent of prescribers' adherence to principles of rational prescribing of antibiotics in inpatient settings [Section 4.3.4] [Objective 1.3.1.2(xvi)(d)]

- Physician specialists and general practitioners observed to an equal extent, but less than surgical consultants, principles of antibiotic prescribing requiring prescribers to seek and know the identity and morphological characteristics of infecting bacteria before prescribing antibiotics.
- Prescribers in inpatient settings violated most antibiotic prescribing principles requiring that specimens from sites of infections be taken and sent to laboratories for culture sensitivity testing before initiation of antibiotic therapy and not after it.
- Prescribers characteristically prescribed antibiotics on trial and error basis only to request for culture sensitivity tests when treatment had failed.
- Physician specialists and general practitioners in comparison with surgical consultants violated most principles of antibiotic prescribing with reference to time of requesting for culture sensitivity tests and revisions of initially prescribed empiric antibiotic therapies following availability of culture sensitivity test results. Physician specialists and general practitioners for these reasons were considered most likely to prescribe antibiotics inappropriately based on violation of these principles.
- Antibiotic prescriptions which would be appropriately and inappropriately written according to the extent to which prescribers within study site inpatient settings

observed principles of antibiotic prescribing were estimated to be in the ratio of 1: 1.33 (Table 4.3.24) which, by considerations of criteria used in assessing prescriptions, correlates with the ratio of 1:1.49 (Table 4.1.1) of appropriately to inappropriately assessed prescriptions determined from results of study Phase I.

- Inappropriate prescribing of antibiotics based on prescribers' violation of principles of antibiotic prescribing within inpatient settings was predicted to be more prevalent in medical than surgical wards based on the extent to which physician specialists and general practitioners had been seen to violate these principles.

5.4.6 Reasons for prescriber's non-request for laboratory assisted information in the prescription of antibiotics [Section 4.3.4] [Objective 1.3.1.2(xvi)(e)].

- The study identified and documented the following as major factors contributing to prescribers' failure to request for rapid microscopic identification of pathogens before initiating empiric antibiotic treatments. These include the following:
  - Deficiencies in operational systems of microbiology laboratories at study sites. This has been noted as contributing to results of laboratory investigations not being provided to prescribers in time to aid in their appropriate choices of antibiotics in empiric treatment of infections. It is presumably a cause of prescribers' disinterest in requesting and failure to request for rapid microscopic identification of pathogens before initiating empiric antibiotic treatments.
  - Heavy prescriber workload with its attendant reduced prescriber-patient contact time. The factor is seen to have a deleterious effect on respondents' ability to effectively diagnose infections including, where appropriate, requesting for rapid microbial identification of morphological characteristics of bacterial pathogens prior to antibiotic prescribing as required by principle in the appropriate targeting of infecting pathogens.
- Based on times that they make available to respondents results of requests for rapid microscopic identification of infecting pathogens, Maluti hospital microbiology laboratory was seen to be the most "efficient" among microbiology laboratories of all five study site hospitals.

5.4.7 Assessment of prescribers' knowledge in principles of antibiotic selection and prescribing [Section 4.3.5] [Objective 1.3.1.2(xvi)(f)]

- Lack of adequate knowledge in bacteriology of infections and principles of appropriate prescribing of antibiotics exists among prescribers and was exhibited by all qualification groups of prescribers, particularly the surgical consultant and nurse qualification groups.
- Specifically prescribers were seen to lack knowledge significantly in
  - their recognition of signs and symptoms of bacterial infections and of bacterial pathogens associated with upper and lower respiratory tract and non-sexually transmitted urinary tract infections resulting in determinations of low probabilities of 0.11, 0.31 and 0.27 of antibiotics being prescribed appropriately and hence would be predictive of high chances of inappropriate prescribing of antibiotics for these infections.
  - antimicrobial properties of antibiotics to enable their selections of antibiotics most appropriately for the treatment of given infections from lists of available antibiotics even if they are provided with information on the morphological characteristics of infecting organisms.
- Doctors demonstrate higher knowledge in the characteristics of bacterial pathogens and antibacterial agents than nurses but have not necessarily been seen to be better prescribers of antibiotics than the latter when compared at the same level of health care delivery.
- No associations, either positive or negative, have been established between prescribers' knowledge in bacteriology of infections and principles of antibiotic prescribing and the extent to which they write antibiotics appropriately. Positive associations of prescribers' knowledge in bacterial infections of the respiratory and urinary tract and appropriateness of antibiotic prescriptions they write have however been shown to exist, though the impact of such associations on appropriateness of antibiotic prescriptions for these infections needed to be proved by further studies. By this finding and according to WHO Global Strategy for Containment of Antimicrobial Resistance (WHO, 2001:25), lack of knowledge in bacteriology and principles of antibiotic prescribing among prescribers is seen as a major factor contributing to inappropriate prescribing of antibiotics in Lesotho.

5.4.8 Costs of antibiotics and pathogen antibiotic sensitivity patterns as factors influencing respondents' choices of antibiotics [Section 4.3.5] [Objective 1.3.1.2(xvi)(g)]

- Prescribers generally do not consider antibiotic costs as a factor in the selection of the agents in treating infections though they were seen to appreciate the importance of the factor in antibiotic selections. On the basis of no significant differences existing in costs of antibiotics used in Lesotho, antibiotic costs indeed is considered not an important factor expected to influence prescribers' decisions in making antibiotic choices.
- Prescribers generally claimed an influence of pathogen sensitivity patterns as a factor as they make their choices of antibiotics but claims of such influences are considered rather more of their appreciation of the importance they attach to the factor than of its application in antibiotic prescribing. Their performance in a knowledge test on the subject largely proved they did not have the required knowledge for doing this in the empiric prescribing of antibiotics.
- Patient and drug related factors such sites of infections, sensitivities of patients to given antibiotics and antibiotic dosage regimens considerations have been indicated by respondents and as such considered as factors influencing prescribers' choice of antibiotics as cited by respondents, are important factors to consider in making choices of antibiotics in treating infections.

5.4.9 Antibiotic stock unavailability as a factor influencing respondents' ability to select antibiotics of choice [Section 4.3.6] [Objective 1.3.1.2(xvi)(h)]

- Antibiotic stock unavailability is confirmed by as many as 84.3% of respondents as limiting their choices of antibiotics to various the extent and is thus considered as a factor influencing prescribers' ability to prescribe their choices of antibiotics.
- The prescription of alternative choices of antibiotics to substitute prescribers' first choices of the drugs in events of stock unavailability is the norm at all study sites and is seen as fomenting inappropriate prescribing of antibiotics in absence of convincing capability of prescribers to make such substitutions on the basis of their knowledge of the comparative therapeutic efficacies of such first and alternative choice antibiotics as determined by their antimicrobial properties.

5.5 Limitations in the use of study results

The study has provided an authentic novel method and means of evaluating the appropriateness of patterns of antibiotic prescribing in public health institutions and also of selecting antibiotics appropriately for cost-effective treatment of infections based on knowledge of sensitivities of bacterial isolates associated with given infections to formulary antibiotics. In spite of the claimed authenticity of formulae and procedures derived for selecting antibiotics in the empiric treatment of infections, antibiotics selected by these procedures as outlined in results may not be used as most preferred antibiotics in treating indicated infections. Doubts on the quality of the culture sensitivity test results data used in determining the parameters employed in the selection process was considered to negatively affect the calculated values for these parameters and as such seen to disadvantage their usefulness practically. Laboratories of study site hospitals as mentioned in Section 4.2, made decisions on which pathogens to test for their sensitivities and against which antibiotics in a haphazard manner which resulted in the generation of culture sensitivity test result data used in the determinations not seen to be reflective of the true incidences of isolation of pathogens and their determined percentage sensitivities against antibiotics.

Also of importance is the observation that specimens sent to laboratories for culture sensitivity testing were obtained only in cases of treatment failures following initial antibiotic treatments. Culture sensitivity test results data used for the determinations are for this reason considered a subset data that excludes data on what could provide information on the frequencies of isolation of pathogens and their sensitivities to antibiotics from specimens of infections that were successfully treated with initially prescribed antibiotics. These noted limitations of the study are to some extent seen to compromise the integrity of results of the phase of the research based on culture sensitivity test data analysis and may not particularly, enable the complete adoption for practical use of the antibiotics selected for preferential treatment of indicated infections as recommended.

Manners of antibiotic prescribing for infections with possible bacterial aetiologies, though may be done appropriately in accordance with principles of rational antibiotic prescribing, may not be therapeutically beneficial if antibiotics prescribed in such circumstances happen to be for infections with aetiological agents other than bacterial pathogens. Significantly, this implies that the practice of writing antibiotic prescriptions for possible

infections even if done appropriately constitutes a problem for which prescribers' adherence to principles of empiric prescribing of antibacterial agents alone does not offer a solution.

Irrespective of the above limitations the results of the study are seen as providing baseline information that raised curtains on problems inherent in antibiotic prescribing in Lesotho. In itself, the research provides a novel approach to antibiotic prescription assessment for performance evaluation and antibiotic selection for effective treatment of infections and serves as model for future studies that could be done to produce results for practical use in improving antibiotic prescribing for more cost-effective treatment of infections.

5.6 Recommendations

Results of this research in its three-phase design showed that a majority of prescriptions assessed for their appropriateness have been inappropriately prescribed, and that appropriate prescribing of antibiotics have a positive impact on treatment outcomes and costs of antibiotic treatment. It also attributed lack of adequate knowledge in bacteriology and principles of appropriate antibiotic prescribing as a major factor contributing to the unsatisfactory manner in which antibiotics are prescribed at study site hospitals. On the basis of these results, the following are recommended as necessary steps that could be taken to improve antibiotic prescribing at study site hospitals and other hospitals in the country, to ensure that optimum therapeutic and cost benefits are derived from the use of these drugs in the treatment of infections.

5.6.1 Improving culture sensitivity data quality for future studies

It is recommended that the Ministry of Health and Social Welfare (MOH & SW), through its Clinical and Pharmaceutical Services unit, set up a mechanism of appropriate procedures of culture sensitivity testing of pathogens against formulary antibiotics to create a creditable data base of culture sensitivity test results that could be analysed when needed, to obtain valid information on patterns of bacterial pathogen sensitivities to antibiotics necessary for decision making in antibiotic use. Such creditable and authentic data on bacterial pathogen sensitivities, for example, would be necessary,

even essential, for use in determining changes in resistance patterns of pathogens to antibiotics and in providing data for antibiotic selections in cost-effective empiric treatment of infections by using formula derived from this study.

5.6.2 Improving procedures of infection diagnosis and antibiotic prescribing for quality management of patients for infections

The activities listed below, also to be directed by the Clinical and Pharmaceutical Services unit of MOH&SW, are recommended for improving procedures of infection diagnosis and antibiotic prescribing.

- Creation of a task force of experts on antibiotic prescribing to formulate policies on the diagnosis and treatment of infections to ensure the proper use of antibiotics in the country for attainment of improved treatment outcomes while avoiding misuse of the drugs and accompanying adverse results of resistance development.
- Conduction of continuous education programmes in the form of seminars and workshops for prescribers on antibiotic prescribing with focus on
  - antibiotics and their characteristics;
  - bacteriology of infections from perspectives of associations of bacterial pathogens with infections they cause;
  - principles of antibiotic prescribing;
  - antibiotic selection in the empiric treatment of infections based on local antibiotic sensitivity patterns of bacterial pathogens; and
  - methods of diagnosing infections and establishing need for antibiotic use prior to prescribing these agents.
- Development of local antibiograms for use in antibiotic selection for various infections
- Development of algorithms of infection diagnosis and guidelines for antibiotic prescribing for prescribers' references as they diagnose and treat infections.

5.6.3 Changes of antibiotic prescription protocols

The following recommendations are subject to a review to be based on results of a repeat study of Phase II of this research using culture sensitivity test results data

generated in a manner that avoids limitations identified as compromising the validity of current data used for this study.

- For purposes of improving treatment outcomes of infections prescribers' adherence to basic principles of antibiotic prescribing for inpatients is highly recommended. This, among others, requires for initial empiric antibiotic prescriptions to be revised based on results of culture sensitivity tests performed on specimens sent to laboratories prior to initiation of antibiotic therapy.

- Patterns of antibiotic prescribing as established by findings of the study documented ampicillin or amoxycillin and co-trimoxazole as most frequently empirically prescribed antibiotics in outpatient departments amidst findings of their low percentage activities against bacterial pathogens locally implicated as aetiological agents in many infections. Except for respiratory tract infections where a calculated 69.0% percentage overall activity (POA) may allow for its empiric prescription in established bacterial infections of the tract, it is recommended to curtail the empiric prescription of ampicillin or amoxycillin in the majority of infections in favour of antibiotics with higher percentage activities against pathogens. This is particularly recommended in cases where gram-negative organisms are target pathogens of treated infections. The same recommendation is made for the overwhelming use of co-trimoxazole in treating infections including gastroenteritis.

- *Staphylococcus aureus* is dominantly and *Staphylococcus epidermidis* moderately associated with lower respiratory tract infections among inpatients. The former pathogen is also strongly associated with throat infections (Section 4.2.2, Table 4.2.3). In the light of this and also in the light of local antibiotic sensitivity patterns of bacterial pathogens suggesting that ampicillin and co-trimoxazole are ineffective in treating staphylococci infections, the dominant prescribing of these antibiotics in the empiric treatment of respiratory tract infections as study results showed, is not considered effective. In view of this finding it is recommended that current empiric antibiotic treatment protocols that prescribers routinely use in treating respiratory tract infections be changed in favour of antibiotic treatment protocols opting for the use of antibiotics selected

on the basis of their overall activities against bacterial pathogens commonly associated with infections of the respiratory tract.

5.6.4 Addressing problems contributing to inappropriate antibiotic prescribing at study sites.

Health policy makers in both CHAL and Government institutions use nurses without the requisite training in diagnosis and treatment of infections in extending clinical services to rural areas. The situation is seen as contributing to inappropriate use of antibiotics in view particularly of the very low levels of knowledge nurses were seen to have in bacteriology of infections and principles of antibiotic prescribing as established by this study. It is recommended that nurses in these qualification categories that are used for these services are given appropriate training in the diagnosis and treatment of infections before they are assigned such extended duties. Use of algorithms in the diagnosis and treatment of common infections at primary health care levels is also recommended. Such algorithms should be developed and nurses particularly trained in their practical use in infection diagnosis and treatment at the levels of health care where clinical services of nurses are employed.

5.6.5 Building capacity for the appropriate prescribing and use of antibiotics: Suggested roles of pharmacists in the implementation of research recommendations

Pharmacists are custodians of drugs and as health professionals they have the responsibility within hospital particularly, to advise other health professionals in the clinical use of drugs, including antibiotics. In this capacity they are considered an appropriate calibre of professionals within Lesotho's health service sector to be relied on to capably play major roles in the drive towards improving antibiotic prescribing in the country as promulgated through implementations of recommendations emanating from results of this research. Within this context they would be found most appropriate to carry out the following responsibilities which are seen as crucial in the implementation of the research recommendations. These include:

- Collation of data from microbiology laboratories of site hospitals on bacterial pathogen sensitivities to formulary antibiotics for the compilation and regular updating of data on antibiotics' percentage overall activities and antibiotic

selection factors for dissemination to prescribers in a bid to improve antibiotic prescribing and use in the country;

- Education of health care workers on antibiotic prescribing and use;
- Auditing of local practices in regard to antibiotic prescribing and use;
- Monitoring antibiotic consumption; and
- helping to develop antibiotic prescribing policies and antibiotic treatment guidelines.

The United Kingdom, according to Weller and Jamiesen (2004:295), can be cited as one example of a country that recognised the roles pharmacists could usefully play in appropriate antibiotic therapy. By this recognition, the UK created positions for pharmacists with interest in infection management with defined responsibilities in its drive to curb the widespread phenomenon of inappropriate prescribing of antibiotics. Variously referred to as "antibiotic pharmacists", "microbiology pharmacists" or "infectious disease pharmacists" these pharmacists operate within the country's health service sector, performing duties that include monitoring of antibiotic use; advising clinicians and educating all grades of health care workers on issues pertaining to appropriate prescribing and use of antibiotics; and help in developing antibiotic prescribing policies. In addition to these, they are entrusted with the responsibility of reviewing all antibiotic prescriptions and also act as secondary sources of advice after the microbiology department (Weller & Jamiesen, 2004:295, 296). As an emulation of this U.K. example of involving pharmacists in antibiotic treatment of patients because of proven benefits of this strategy in antimicrobial therapy, it is recommended that the Lesotho Ministry of Health and Social Welfare institute and encourage the training of pharmacists in infectious disease management to take up the responsibilities of helping to improve antibiotic prescribing and use in the country.

5.7 Recommendation for further studies

Despite the mathematical authenticity of the procedures developed and used in selecting preferred antibiotics in the empiric treatment of infections, it is still considered necessary to validate the practical usefulness of the model as an effective method of selecting antibiotics for the cost-effective treatment of infections. In this regard, it is recommended that further studies be conducted, using real clinical as well as authentic culture

sensitivity data, to establish and compare with other means of antibiotic selection, the therapeutic effectiveness of antibiotics selected and prescribed by the use of the model in treating bacterial infections.

5.8 Chapter summary

Conclusions drawn from evaluations of results of the study in line with the objectives of the research were presented in this chapter. Recommendations which the researcher believed would promote appropriate prescribing of antibiotics were also put forward for consideration by stake holders. This included, among others, roles that Pharmacists play and hence the need for their involvement in efforts to achieve the feat of appropriate prescribing and use of antibiotics.

REFERENCES

ABDI-ALI, A., MOHAMMADI-MEHR, M. & AGHA ALAEI, Y. 2005. Bactericidal activity of various antibiotics against biofilm-producing Pseudomonas aeruginosa. *International journal of antimicrobial agents*, 27:196-200.

ABDUL-HADY, E-G. 1998. Antibiotic prescriptions in primary health care centres. *Inrud news*, 8(2):22-23, Nov.

ABRUTYN, E. 2005a. Botulism. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 842-845.)

ABRUTYN, E. 2005b. Tetanus. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 840-842.)

ABUSIN, S. & JOHNSON, S. 2008. Sulfamethoxazole/Trimethoprim induced liver failure: a case report. *Cases journal*, 1:44.

AGHA, R. & GOLBERG, M.B. 2009. Management of Shigella gastroenteritis. *Update.* http://www.update.com/patients/content/topic.do?topic Date of access: 10 August 2009.

AHLQUIST, D.A. & CAMILLERI, M. 2005. Diarrhoea and constipation. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 224-233.)

AILANI, R.K., AGASTY, A.G., MUKUNDA, B.N. & SHEKAR, R. 1999. Doxycycline is a cost effective therapy for hospitalised patients with community acquired pneumonia. *Archives of internal medicine*, 159:266-270.

AKALIN, H.E. 2002. Surgical prophylaxis: the evolution of guidelines in an era of cost containment. *Journal of hospital infection*, 50 (Supplement A):S3-S7.

AKKERMAN, A.E., KUYVENHOVEN, M.M., VAN DER WOUDEN, J.C. & VERHEIJ, T.J.M. 2005. Analysis of under-and over prescribing of antibiotics in acute otitis media in general practice. *Journal of antimicrobial chemotherapy*, 56:569-574.

ALDRIDGE, A. & LEVINE, K. 2001. Surveying the social world: principles and practice in survey research. Buckingham: Open University Press. 194 p.

ALI, M.H., KALIMA, P. & MAXWELL, S.R.J. 2006. Failure to implement hospital antimicrobial prescribing guidelines: a comparison of two UK academic centres. *Journal of antimicrobial chemotherapy*, 57:959-962.

ALVES, D.A., CUNHA, A.J.L., AMARAL, J. & FONTENELE, E. & SILVA, M.A. 2003. Inappropriate antibiotic prescription to children with acute respiratory infection in Brazil. *Indian pediatrics*, 40:7-12.

AMBROSE, P.G., GRASELA, D.M., GRASELA, T.H., PASSARELL, J., MAYER, H.B. & PIERCE, P.F. 2001. Pharmacodynamics of fluoroquinolones against *Streptococcus pneumoniae* in patients with community-acquired respiratory tract infections. *Antimicrobial agents and chemotherapy*, 45(10):2793-2797.

AMSDEN, G.W. 2001. Advanced generation macrolides: tissue directed antibiotics. *International journal of antimicrobial agents*, 18:S11-S15.

ANDRESEN, L., BOUD, D. & COHEN, R. 1995. Experienced based learning. (*In* Foley, G., *ed.* Understanding adult education and training. Sydney: Allen & Unwin. p. 225-239.)

ANZUETO, A. & NORRIS, S. 2004. Clarithromycin in 2003: sustained efficacy in an era of rising antibiotic resistance. *International journal of antimicrobial agents,* 24:1-17.

APISARNTHANARAK, A., DANCHAIVIJITR, S., KHAWCHAROENPORN, T., LIMSRIVILAI, J., WARACHAN, B., BAILEY, T.C. & FRASER, V.J. 2006. Effectiveness of education and an antibiotic control programme in a tertiary care hospital in Thailand. *Clinical infectious disease*, 42:768-775.

APPELBAUM, P.C. 2007. Reduced glycopeptide susceptibility in methicillin resistant Staphylococcus aureus (MRSA). *International journal of antimicrobial agents*, 30:398-408.

APPELBAUM, P.C., HUNTER, P.A., 2000. The new fluoroquinolone antibacterial agent: past, present and future perspectives. *International journal of antimicrobial agents*, 16(1):5-15.

ARANCIBIA, F., BAUER, T.T., EWIG, S., MENSA, J., GONZALEZ, J. NIEDERMAN, M.S., TORRES, A. 2002. Community-acquired pneumonia due to gram-negative bacteria and *Pseudomonas aeruginosa*. *Archives of internal medicine*, 162:1849-1858.

ARCHER, G.L. & POLK, R.E. 2005. Treatment and prophylaxis of bacterial infections. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 789-806.)

ARCHIBALD, L.K. & REILLER, L.B. 2001. Clinical microbiology in developing countries. *Emerging infectious diseases*, 7(2):302-304.

ARONSON, J.K. 2004. Editors' view: Rational prescribing, appropriate prescribing. *British journal of clinical pharmacology*, 57(3):229-230.

ARRIFIN, H., NAVARATNAM, P., MOHAMED, M., ARASU, A., ABDULLAH, W.A. & LEE, C.L. 1999. Ceftazidime-resistant Klebsiella pneumoniae bloodstream infection in children with febrile neutropenia. *International journal of infectious diseases*, 4:21-24.

ASCAP. Panel Members. 2003. Community-acquired pneumonia: evidence-based antibiotic selection and outcome effective patient management - year 2003 update. *Hospital medicine consensus reports*. http://www.ahcpub.com/ahc_root_htm/hot.archive/ascap2003.html Date of access: 6 December 2004.

ASSISI, F.C. s.a. The great brain robbery. http://www.indolink.com/displayArticles.php?id=062704064115 Date of access: 24 August 2004.

ATIF, A.A., OSMAN, H., MANSOUR, A.M., MUSA, H.A., AHMED, A.B., K.ARRAR, Z. & HASSAN, S.H. 2000. Antimicrobial agent resistance in bacterial isolates form patients with diarrhoea and urinary tract infection in the Sudan. *American journal of tropical medicine and hygiene,* 63(5):259-263.

AUSTEN, K.F. 2005. Allergies, anaphylaxis and systemic mastocytosis. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds*. Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 1947-1956.)

ANZUETO, A., NORRIS, S. 2004. Clarithromycin in 2003: sustained efficacy and safety in an era of rising antibiotic resistance. *International journal of antimicrobial agents*, 24:1-17

BABIC, M., HUJER, A.M. & BONOMO, R.A. 2006. What is new in antibiotic resistance? Focus on beta-lactamases. *Drug resistance updates*, 9:142-156.

BADRI, M., EHRLICH, R., WOOD, R. & MAARTENS, G. 2001. Initiating cotrimoxazole prophylaxis in HIV -infected patients in Africa: and evaluation of the provisional WHO/UNSAIDS recommendation. *AIDS*, 15:1143-1148.

BALAGOPAL, A. & SEARS, C.L. 2007. Clostridium difficile: new therapeutic options. *Current opinion in pharmacology*, 7:455-458.

BALL, P., BAQUERO, F., CARS. O., FILE, T., GARAU, J., KLUGMAN, K., LOW, D.E., RUBISTEIN, E. & WISE, R. 2002. Antibiotic therapy of community respiratory tract infections: strategies for optimal outcomes and minimised resistance emergence. *Journal of antimicrobial therapy,* 49:31-40.

BANNISTER, B.A., BEGG, N.T. & GILLESPIE, S.H. 2000. Infectious disease. 2nd ed. Oxford: Blackwell Science. 506 p.

BARBOSA, T.M. & LEVY, S.B. 2000. The impact of antibiotic use on resistance development and persistence. *Drug resistance updates*, 3:303-311.

BARTLETT, J.G., DOWELL, S.F., MANDEL, L.A., FILE, JR T.M., MUSHER, D.M., FINE, M.J. 2000. Practice guidelines for the management of community acquired pneumonia in adults: Infectious Disease Society of America. *Clinical infectious disease*, 31 (2) 347 -382.

BEHRA-MIELLET,. J., DUBREUIL, L., JUMAS-BILAK, E. 2002. Anaerobic activity of moxifloxacin compared with that of ofloxacin, ciprofloxacin, clindamycin, metronidazole and β-lactams. *International journal of antimicrobial agents*, 20(5):366-374.

BERTINO, J., Jr. & FISH, D. 2000. The safety profile of the fluoroquinolones. *Clinical therapeutics*, 22(7):798-817.

BISHT, R., KATIYAR, A., SINGH, R. & MITTAL, P. 2009. Antibiotic resistance - a global issue of concern. *Asian journal of pharmaceutical and clinical research,* 2(2):34-39.

BISHAI, W. 2002. Current issues on resistance, treatment guidelines and the appropriate uses of fluoroquinolones for respiratory tract infections. *Clinical therapeutics*. 24(6):838-850.

BITNER-GLINDZICZ, M. & RAHMAN, S. 2007. Ototoxicity caused by aminoglycosides is severe and permanent in genetically susceptible people. *British medical journal,* 7624:784-785.

BLANDINO, G., MARCHESE, A., ARDITO, F., FADDA, G., FONTANA, R., CASCIOLO, G., MARCHETTI, F., SCHITO, G.C. & NICOLETTI, G. 2004. Antimicrobial susceptibility profiles of *Pseudomonal aeruginosa* and Staphylococcus aureus. *International journal of antimicrobial agents*, 24:515-518.

BLASI, F., EWIG, S., TORES, A. & HUCHON, G. 2006. A review of guidelines for antibacterial use in acute exacerbations of chronic bronchitis. *Pulmonary pharmacology and therapeutics*, 19:361-369.

BLONDEAU, J.M. 1999. Expanded activity and utility of the new fluoroquinolones: a review. *Clinical therapeutics*, 21(1):3-40.

BLONDEAU, J.M. & TILLOTSON, G.S. 1999. Formula to help select rational antimicrobial therapy (FRAT): its application to community and hospital acquired urinary tract infections. *International journal of antimicrobial agents*, 12(2):145-150.

BOWLER, P.G., DUERDEN, B.I., ARMSTRONG, D. G. 2001. Wound microbiology and associated approaches to wound management. Clinical microbiology reviews, 14(2):244-269.

BOLOHNIA, J.L. & BRAVERMAN, I.M. 2005. Skin manifestations of internal disease. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 296-318.)

BOSKER, G. s.a. Antibiotic selection in emergency medicine. http:/www.thrombosis-consult.com/articles/textbook/30_antibioticupdate.htm. Date of access: 19 June 2004

BOSTIAN, K., GLINKA, T., LOMOVSKAYA, O., SURBER, M., BERKLEY, N. & GRIFFITH, D. 2008. Bacterial efflux pump inhibitors for the treatment of ophthalmic and otic infections. Patent: US 2008/0132457 a1. 1 p.

BOWLER, P.G., DUERDEN, B.I. & ARMSTRONG, D.G. 2001. Wound microbiology and associated approaches to wound management. *Clinical microbiology reviews*, 14(2):244-269.

BRADFORD, P.A. 2004. Tigecycline: a first in class glycylcycline. *Clinical microbiology newsletter,* 26(21):163-168.

BRATZLER, D.W. & HOUCK, P.M. 2005. Antimicrobial prophylaxis for surgery: an advisory statement from the national surgical infection prevention project. *American journal of surgery,* 189:395-404.

BRITISH MEDICAL ASSOCIATION & ROYAL PHARMACEUTICAL SOCIETY OF GREAT BRITAIN. 2003. Quinolones. *British National Formulary*, 44:294.

BRITTEN, N., JENKINS, L., BARBER, N., BRADLEY, C. & STEVENSON, F. 2003. Developing a measure for the appropriateness of prescribing in general practice. *Quality and safety in health care*, 12:246-250.

BRONSKA, E., KALMUSOVA, J., DZUPOVA, O., MARESOVA, V., KRIZ, P. & BENES, J. 2006. Dynamics of PCR based diagnosis in patients with invasive meningococcal disease. *Clinical microbiology and infection,* 12(2):137-141.

BROWN, E.M. 2002. Guidelines for antibiotic usage in hospitals. *Journal of antimicrobial chemotherapy*, 49(4):587-592.

BROWN, P.D. & NGENO, C. 2007. Antimicrobial resistance in clinical isolates of Staphylococcus aureus in Southern Jamaica. *International journal of infectious diseases*, 11:220-225.

BRYMAN, A. 2004. Social research methods. 2nd ed. New York: Oxford University Press. 540 p.

BURKE, J.P. 2001. Maximizing appropriate antibiotic prophylaxis for surgical patients: an update from LDS hospital, Salt Lake City. *Clinical infectious diseases,* 33(Suppl 2):S78-S83.

BUTLER, K.H., REED, K.C. & BOSKER, G. s.a. PC textbook - urinary tract infections: diagnosis and evaluations. p. 1-30. http:/www.hypertension-consult.com/Secure/ textbookarticles/Primary_Care_Book/38.htm Date of access: 19 June 2004

BUTTERTON, J.R. & CALDERWOOD, S.B. 2005. Acute infectious diarrheal diseases and bacterial food poisoning. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 754-759.)

BUYNAK, J.D. 2006. Understanding longevity of the β-lactam antibiotics and of antibiotic/β-lactamase-inhibitor combinations. *Biochemical pharmacology*, 71:930-940.

CADIEUX, G., TAMBLYN, R., DAUPHINEE, D. & LIBMAN, M. 2007. Predictors of inappropriate antibiotic prescribing among primary care physicians. *Canadian Medical Association journal,* 177(8):877-883.

CARNIEL, E. 2001. The Yersinia high-pathogenicity island: an iron uptake island. *Microbes of infection*, 3(7): 561-569.

CASADEVALL, A. & PIROFSKI, L. 1999. Host-pathogens interactions: redefining the basic concepts of virulence and pathogenicity. *Infection and immunity*, 67(8):3703-3713.

CASADEVALL, A. & PIROFSKI, L. 2000. Host-pathogens interactions: basic concepts of microbial commensalisms, colonisation, infection and disease. *Infection and immunity*, 68(12):6511-6518.

CHAMANY, S., SCHULKIN, J., ROSE, C.E., Jr., RILEY, L.E. & BESSER, R.E. 2005. Knowledge, attitudes and reported practices among obstetrician-gynaecologists in the USA regarding antibiotic prescribing for upper respiratory tract infections. *Infectious disease in obstetrics and gynaecology*, 13(1):17-24.

CHAMBERS, H.F. 2001. Antimicrobial agents. (*In* Hardman, J.G. & Limbird, L.E., *eds.* The pharmacological basis of therapeutics. 10th ed. New York: McGraw-Hill. p. 1143-1266.)

CHANG, F.E., YU, W.L. 2005. Legionella infection. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 870-874.)

CHANG, W.C., LI, R.C., LING, J.M., CHENG, A.F. & SCHENTAG, J.J. 1999. Markedly different rates of resistance profiles exhibited by seven commonly used and newer β-lactams on the selection of resistant variants of *Enterobacter cloacae. Journal of antimicrobial chemotherapy*, 34:55-60.

CHEESBROUGH, M. 2000. District laboratory practice in tropical countries. Cambridge: Cambridge University Press. 434 p.

CHEN, Y., HUANG, W.G., ZHA, D.J., QIU, J.H., WANG, J.L., SHA, S.H. & SCHACHT, J. 2007. Aspirin attenuates gentamicin ototoxicity: from the laboratory to the clinic. *Hearing research*, 226(1-2):178-182.

CHETLEY, A. 1993. The antibiotic crisis: problem drugs. *Health Action International:* 51-56.

CHHIBBER, S., AGGARWAL, S. & YADAV, V. 2003. Contribution of capsular and lipopolysaccharide antigens to the pathogenesis of *Klebsiella pneumoniae* respiratory tract infection. *Folia microbiologica*, 48(5):699-702.

CHOPRA, I. 2002. New developments in tetracycline antibiotics: glycylcyclines and tetracycline efflux pump inhibitors. *Drug resistance updates*, 5:119-125.

COHEN, J. 1988. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, N.J.: Erlbaum. 567 p.

COLGAN, R. & POWERS, J. 2001. Appropriate antibiotic prescribing: approaches that limit antibiotic resistance. *American family physician,* 64(6):999-1004.

COLLINI, P., BEADSWORTH, M., ANSON, J., NEAL, T., BURNHAM, P., DEEGAN, P., BEECHING, N. & MILLER, A. 2007. Community-acquired pneumonia: doctors do not follow national guidelines. *Post graduate medical journal*, 83:552-555.

CONNOLLY, G.M., DRYDEN, M.S., SHANSON, D.C. & GAZZARD, B.G. 1988. Cryptosporidial diarrhoea in AIDS and its treatment. *British medical journal*, 29:593-597.

CONTRERAS-MARTEL, C., JOB, V., GULMI, A.M.D., VERNET, T., DIDEBERG, O. & DESSEN, A. 2006. Crystal structure of penicillin binding protein 1a (PBP1a) reveals a mutational hotspot implicated in β-lactam resistance in *Streptococcus pneumoniae. Journal of molecular biology,* 355:684-696.

CORBEL, M.J. & BEECHING, N.J. 2005. Brucellosis. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 914-917.)

CROSS, J.T., Jr. 2001. Fluoroquinolones. *Seminars in pediatric infections diseases,* 12(3):211-223.

ČULIĆ, O., ERAKOVIĆ, V. & PARNHAM, M.J. 2001. Anti-inflammatory effects of macrolide antibiotics. *European journal of pharmacology*, 429:209-229.

DALHOFF, A., JANJIC, N. & ECHOLS, R. 2006. Redefining penems. *Biochemical pharmacology*, 71:1085-1095.

DAROUICHE, R.O. 2001. Device associated infections: a macroproblem that starts with microadherence. *Clinical infectious diseases*, 33:1567-1572.

DARVILLE, T. 1999. Imipenem and Meropenem. *Seminars in pediatric infectious diseases,* 10(1):38-44.

DAWSON, C. 2006. A practical guide to research method: a user-friendly manual for mastering research techniques and projects. 2nd ed. Oxford: How To Books. 157 p.

DAZA, R., GUTIERREZ, J. & PIEDROLA, G. 2001. Antibiotic susceptibility of bacterial strains isolated from patients with community-acquired urinary tract infections. *International journal of antimicrobial agents*, 18:211-215.

DENNIS, D.T. & CAMBELL, G.L. 2005. Plague and other yersinia infections. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds*. Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 921-929.)

DENNO, D.M., FRIMPONG, E., GREGORY, M. & STELL, R.W. 2002. Nasopharyngeal carriage and susceptibility patterns of *Streptococcus pneumoniae* in Kumasi, Ghana. *West African journal of medicine*, 21(3):233-236.

DEPARTMENT OF PHARMACY **see** QUEEN II HOSPITAL. Department of Pharmacy

DERENDORF, H. 2010. Impression on formula and procedures developed by M. Adorka for the empiric selection of antibiotics. (Written comments in possession of the author.)

DOAN, T., FUNG, H.B., MEHTA, D. & RISKA, P.F. 2006. Tigecycline: a glycylcycline antimicrobial agent. *Clinical therapeutics*, 28(8):1079-1106.

DOI, Y. & ARAKAWA, Y. 2007. 16s Ribosomal RNA methylation: emerging resistance mechanism against aminoglycosides. *Clinical infection infectious diseases*, 45:88-94.

DOLIN, R. 2005. Common respiratory infections and severe acute respiratory syndrome. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds*. Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 1059-1064.)

DOUGHERTY, T.J., BEAULIEU, D. & BARETT, J.F. 2001. New quinolones and the impact on resistance. *Drug discovery today,* 6(10):529-536.

DREW, R.H. 2008. Prevention and treatment of infectionsin Neutropenic cancer patients. (*In* Koda-Kimble, M.A., Young, L.Y., Alldredge, B.K., Corelli, R.L., Guglielmo, B.J., Kradjan, W.A. & Williams, B.R., *eds*. Applied therapeutics: the clinical use of drugs. 9th ed. Philadelphia, Pa.: Wolters Kluwer Health/Lippincott & Wilkins. p. 68-1 - 68-18.)

DRINKOVIC, D., FULLER, E.R., SHORE, K.P., HOLLAND, D.J. & ELLIS-PEGLER, R. 2001. Clindamycin treatment of Staphylococcus aureus expressing inducible clindamycing resistance. *Journal of antimicrobial chemotherapy*, 48:315-329.

DROMIGNY, J.A., MACONDO. E.A., JUERGENS-BEHR, A., SILBY, T., PERRIER-GROS-CLAUDE, J.D. 2004. The distribution and antibiotic susceptibility of Shigella isolates in Dakar, Senegal (2000-2002). *International journal of antimicrobial agents*, 24(3):307-308.

DUBBERKE, E.R. & FRASER, V. 2005. Cycling and other strategies to slow and reverse antibiotic resistance. http://www.medscape.com/viewarticle/494369. Date of access: 15 August 2009.

DURSO, S.C. 2005. Oral manifestations of disease. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 194-201.)

ELLIOT, T., HASTINGS, M. & DESSELBERGER, U. 2004. Lecture notes on medical microbiology. 3rd ed. Oxford: Blackwell Science. 311 p.

ERAUT, M. 2004. Informal learning at the work place. *Studies in continuing education,* 26(2):247-273.

ERBAY, A., BODUR, H., AKINCI, E. & ÇOLPAN, A. 2009. Evaluation of antibiotic use in intensive care units of a tertiary care hospital in Turkey. *Journal of hospital infection,* 59(1):53-61.

ERIKSEN, H.M., CHUGULU, S., KONDO, S. & LINGAAS, E. 2003. Surgical infections at Kilimanjaro Christian Medical Centre. *Journal of hospital infection*, 55:14-20.

ERWIN, M.E., FIX, A.M. & JONES, R.N. 2001. Three independent yearly analyses of the spectrum and potency of metronidazole: a multi-centre study of 1,108 contemporary anaerobic clinical isolates. *Diagnostic microbiology and infectious disease*, 39:129-132.

ESCRIBANO, I., RODRIGUEZ, J.C., CEBRIAN, L. & ROYO, G. 2004. The importance of efflux systems in the quinolone resistance of clinical isolates of Salmonella. *International journal of antimicrobial agents,* 24:428.

FARIÑAS, M.C., PÉREZ-VÁZQUEZ, A., FARINAS-ÁLVAREZ, C., GARCÍA-PALOMO, J.D., BERNAL, J.M., REVUELTA, J.M. & GONZÁLEZ-MACÍAS, J. 2006. Risk factors of prosthetic valve endocarditis: a case control study. *Annals of thoracic surgery,* 81:1284-1290.

FEIKIN, D.R., STHUCHAT, A., KOLCZAK, M., BARRETT, M.S., HARRISON, L.H., LEFKOWITZ, L., McGEER, A., FARLEY, M.M., VUGIA, D.J., LEXAU, C., STEFONEK, K.R., PATTERSON, J.E. & JORGENSEN J.H. 2000. Mortality from invasive pneumococcal pneumonia in the era of antibiotic resistance - 1995 -1997. *American journal of public health*, 90(2):223-229.

FELMINGHAM, D., FARELL, D.J., REINER, T.R. & MORRISSEY, J. 2004. Antibacterial resistance among children with community-acquired respiratory tract infections (PROTEKT 1999 - 2000). *Journal of infection*, 48:39-55.

FERRARA, A.M. 2007. Treatment of hospital-acquired pneumonia caused by methicillin resistant Staphylococcus aureus. *International journal of antimicrobial agents*, 30:19-24.

FERRARA, G., LOSI, M., FRANCO, F., CORBETTA, L., FABBRI, L.M. & RICHELDI, M. 2005. Macrolides in the treatment of asthma and cystic fibrosis. *Respiratory medicine,* 99:1-10.

FILE, T.M. 2005. Telithromycin: new product overview. *Journal of allergy and clinical immunology*, 115(2):S361-S373.

FINCH, R. 2005. Antimicrobial therapy: principles of use. *Medicine*, 33(3):42-46.

FISH, N.G. 2008. Urinary tract infections. (*In* Koda-Kimble, M.A., Young L.Y., Alldredge, B.K., Corelli, R.L., Guglielmo, B.J., Kradjan, W.A. & Williams, B.R., *eds.* Applied therapeutics: the clinical use of drugs. 9th ed. Philadelphia, Pa.: Wolters Kluwer Health/Lippincott & Wilkins. p. 64-1 - 64-23.)

GALIMAND, M., COURVALIN, P. & LAMBERT, T. 2003. Plasmid-mediated high level resistance to aminoglycosides in Enterobacteriaceae due to 16S rRNA methylation. *Antimicrobial agents and chemotherapy*, 47(8):2565-2571.

GARAU, J. & DAGAN, R. 2003. Accurate diagnosis and appropriate treatment of acute bacterial rhinosinusitis: minimising bacterial resistance. *Clinical therapeutics*, 25(7):1936-1951.

GAUR, A.H. & ENGLISH, B.K. 2006. The judicious use of antibiotics - an investment towards optimised health care. *Indian journal of paediatrics*, 73(4):343-350.

GAUR, A.H., HARE, M.E. & SHORR, R.I. 2005. Provider and practice characteristics associated with antibiotic use in children with presumed viral respiratory tract infections. *Pediatrics*, 115(3):635-641.

GEARHART, S.L. & BULKLEY, G. 2005. Common diseases of the colon and anorectum and mesenteric vascular insufficiency. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds*. Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 1795-1808.)

GELBER, R.H. 2005. Leprosy (Hansen's disease). (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds*. Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 966-971.)

GELFAN, J.A. & CALLAHAN, M.V. 2005. Fever of unknown origin. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds*. Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 116-121.)

GELONE, P.S. & O'DONNELL, J. 2008. Respiratory tract infections. (*In* Koda-Kimble, M.A., Young, L.Y., Alldredge, B.K., Corelli R.L., Guglielmo, B.J., Kradjan, W.A. & Williams, B.R., *eds*. Applied therapeutics: the clinical use of drugs. 9th ed. Philadelphia, Pa.: Wolters Kluwer Health/Lippincott & Wilkins. p. 60-1 - 60-29.)

GERSHON, A. 2005a. Abdominal swelling and ascites. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds*. Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 243 -246.)

GERSHON, A. 2005b. Mumps. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds*. Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 1154-1155.)

GHOLIZADEH, Y. & COURVALIN, P. 2000. Acquired and intrinsic glycopeptide resistance in enterococci. *International journal of antimicrobial agents*, 16:S11-S17.

GIAMARELLOS-BOURBOULIS, E.J. 2008. Macrolides beyond the conventional antimicrobials: a class of potent immunomodulators. *International journal of antimicrobial agents*, 31(1):12-20.

GILLILAND, W.R. & TSOKOS, G.C. 2002. Prophylactic use of antibiotics and immunisations in patients with SLE. *Annals of rheumatic disease*, 61:191-192.

GINSBURG, A.S., GROSSET, J.H. & BISHAL, W.R. 2003. Fluoroquinolones, tuberculosis and resistance. *Lancet infectious disease*, 3:432-442.

GOAD, J.A. & HESS, K.M. 2008. Sexually transmitted diseases. (*In* Koda-Kimble, M.A., Young, L.Y., Alldredge, B.K., Corelli R.L., Guglielmo, B.J., Kradjan, W.A. & Williams B.R., *eds*. Applied therapeutics: the clinical use of drugs. 9th ed. Philadelphia, Pa.: Wolters Kluwer Health/Lippincott & Wilkins. p. 65-1 - 65-30.)

GOLDSTEIN, E.J.C., CITRON, D.M., VAIDYA, S.A., WARREN, Y.A., TYRRELL, K.L., MERRIAM, C.V. & FERNANDEZ, H. 2006. In vitro activity of 11 antibiotics against 74 anaerobes isolated from paediatric intra-abdominal infections. *Anaerobe,* 12(2):63-66, April.

GONZALES, R., BARTLETT, J.G., BESSER, R.E., HICKNER, J.M., HOFFMAN, J.R. & SANDE, M.A., 2001. Principles of appropriate antibiotic use for treatment of non-specific upper respiratory tract infections in adults: background. *Annals of internal medicine*, 134(6):490-494.

GOULD, I.M. 1999. A review of the role of antibiotic policies in the control of antibiotic resistance. *Journal of antimicrobial chemotherapy*, 43(4):459-465.

GOVERNMENT OF LESOTHO AND THE CHRISTIAN HEALTH ASSOCIATION OF LESOTHO **see** LESOTHO

GRIMWADE, K., STURM, A.W., NUNN, A.J., MBATHA, D., ZUNGU, D. & GILKS, C.F. 2005. Effectiveness of co-trimoxazole prophylaxis on mortality in adults with tuberculosis in rural South Africa. *AIDS*, 19:163-168.

GROSS, P. & PUJAT, D. 2001. Implementing practice guidelines for appropriate anti microbial usage. *Medical care,* 39(8):II-55 - II-69.

GUGLIELMO, B.J. 2008. Principles of infectious diseases. (*In* Koda-Kimble, M.A., Young L.Y., Alldredge, B.K., Corelli, R.L., Guglielmo, B.J., Kradjan, W.A. & Williams B.R., *eds.* Applied therapeutics: the clinical use of drugs. 9th ed. Philadelphia, Pa.: Wolters Kluwer Health/Lippincott & Wilkins. p. 56-1 - 56-24.)

GUGLIELMO, B.J. 1988. Principles of infectious diseases. (*In* Koda-Kimble, M.A., Young L.Y., Alldredge, B.K., Corelli, R.L., Guglielmo, B.J., Kradjan, W.A. & Williams B.R., *eds.* Applied therapeutics: the clinical use of drugs. 9th ed. Philadelphia, Pa.: Wolters Kluwer Health/Lippincott & Wilkins. p. 725-726.)

GULIG, P.A. 2010. Impression on formula and procedures developed by M. Adorka for the empiric selection of antibiotics. (Written comments in possession of the author.)

HAMILTON-MILLER, J.M.T. & SHAH, S. 2000. Patterns of phenotype resistance to the macrolide-lincosamide-ketolide-streptogramin group of antibiotics of antibiotics in staphylococci. *Journal of antimicrobial chemotherapy*, 46:941-949.

HART, A.M. 2007. An evidenced based approach to the diagnosis and management of acute respiratory infections. *Journal for nurse practitioners,* 3(9):607-611.

HEALTH TECHNOLOGY ASSESSMENT UNIT **see** MALASIA. Health Technology Assessment Unit

HENNESSY, T.W., PETERSEN, K.M., BRUDEN, D., PARKINSON, A.J., HURLBURT, D., GETTY, M., SCHWARTZ, B. & BUTLER, J.C. 2002. Changes in antibiotic-prescribing practices and carriage of penicillin-resistant Streptococcus pneumoniae: a controlled intervention in trial in rural Alaska. *Clinical infectious diseases,* 34:1543-1550.

HERA CONSULTANCY **see** LESOTHO. HERA Consultancy final report on Lesotho Pharmaceutical sector review

HOLMES, K.K. 2005. Sexually transmitted diseases: overview and clinical approach. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 762-775.)

HOOHLO, N. 1994. A study of the sensitivity pattern of commonly isolated micro-organisms at Q.E. II Hospital. Maseru: N.H.T.C. (Dissertation - Diploma in Pharmaceutical Technology.) 45 p.

HOOTON, T.M. 2001. Antimicrobial resistance: a plan for action for community practice. *American family physician*, 63(6):1087-1096.

HOPE, R.A., LONGMORE, J.M., McMANUS, S.K. & WOOD-ALLUM, C.A. 1998. Oxford handbook of clinical medicine. 4th ed. Oxford: Oxford University Press. 724 p.

HORTON, J.C. 2005. Disorders of the eye. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds*. Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 162-176.)

HOWARD, S.K., GABA, D.M. 2004. Training fatigue: A renew limits on workhours enough. *Canadian medical association journal*, 170(6):975.

INGLIS, T.J.J. 2003. Microbiology and infection: a clinical core context for integrated curriculum with self assessment. 2nd ed. Edinburgh: Churchill Livingstone. 284 p.

INOUE, M., LEE, N.M., HONG, S.W., LEE, K. & FELMINGHAM, D. 2004. PROTEKT 1999-2000: a multi-centre study of the antibiotic susceptibility of respiratory tract pathogens in Hong Kong, Japan and South Korea. *International journal of antimicrobial agents*, 23:44-51.

JACOBS, M.R. & DAGAN, R. 2004. Antimicrobial resistance among pediatric respiratory tract infections: clinical challenges. *Seminars in pediatric infections diseases*, 15(1):5-20, January.

JACOBS, M.R., FELMINGHAM, D., APPELBAUM, P.C., GRUNEBERG, R.N. & ALEXANDER PROJECT GROUP. 2003. The Alexander project 1998 - 2000: susceptibility of pathogens isolated from community-acquired respiratory tract infection to commonly used antimicrobial agents. *Journal of antimicrobial chemotherapy*, 52:229-246.

JAPONI, A., ALBORZI, A., KALANI, M., NASIRI, J., HAYATI, M. & FARSHAD, S. 2006. Multidrug-resistant bacteria isolated from intensive-care-units patient samples. *Burns*, 32:343-347.

JEELANI, N.U.O., KULKARNI, A.V., DESILVA, P., THOMPSON, D.N.P. & HAYWARD, R.D. 2009. Postoperative cerebrospinal fluid wound leakage as a predictor of shunt infection: a prospective analysis of 205 cases. *Journal of neurosurgery pediatrics*, 4:166-169.

JOHNSON, A.P., LIVERMORE, D.M. & TILLOTSON, G.S. 2001. Antimicrobial susceptibility of Gram-positive bacteria: what is current, what is anticipated? *Journal of hospital infection*, 49(Supplement A):S3-S11.

JONES, M.E., KARLOWSKY, J.A., DRAGHI, D.C., THORNSBERRY, C., SAHM, D.F. & NATHWANI, D. 2003. Epidemiology and antibiotic susceptibility of bacteria causing skin and soft tissue infections in the USA and Europe: a guide to appropriate antimicrobial therapy. *International journal of antimicrobial agents*, 22:406-419.

JONES, R.N., HUYNH, H.K. & BIEDENBACH, D.J. 2004. Activities of doripenem (S-4661) against drug-resistant clinical pathogens. *Antimicrobial agents and chemotherapy*, 48(8):3136-3140.

JONES, R.N. & MANDELL, L.A. 2002. Fluoroquinolones for the treatment of outpatient community-acquired pneumonia. *Diagnostic microbiology and infectious disease*, 44:69-76.

JOSHI, M., BERNSTEIN, J., SOLOMKIN, J., WESTER, B.A. & KUYE, O. 1999. Piperacillin / tazobactam plus tobramycin versus ceftazidime plus tobramycin for the treatment of patients with nosocomial lower respiratory tract infections. *Journal of antimicrobial chemotherapy*, 43:389-397.

JUSTO, D., MARDI, T. & ZELTSER, D. 2004. Roxithromycin-induced torsades de pointes. *European journal of internal medicine*, 15:326-327.

KALRE, I., KONSTABEL, C., BADSTUBNER, D., WERNER, G. & WITTE, W. 2003. Occurrence and spread of antibiotic resistances in *Enterococcus faecium*. *International journal of food microbiology*, 88:269-290.

KARALUS, R. & CAMPAGNARI, A. 2000. Moraxella catarrhalis: a review of an important human mucosal pathogen. *Microbes and infection*, 2:547-559.

KARIUKI, S., REVATI, G., KIIRU, J., LOWE, B., BERKLEY, J.A. & HART, C.A. 2006. Decreasing prevalence of antimicrobial resistance in non-typhoidal salmonella isolated from children with bacteraemia in a rural district hospital, Kenya. *International journal of antimicrobial agents*, 28:166-171.

KASPER, D.L. 2005. Infections due to mixed anaerobic organisms. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 940-946.)

KASPER, D.L. & BARLAM, T.F. 2005. Infections due to HACEK group and miscellaneous gram negative bacteria. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 867-870.)

KASPER, D.L. & MADOFF, L.C. 2005. Gas gangrene and other clostridial infections. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 845-849.)

KASPER, D.L. & ZALEZNIK, D.F. 2005. Intraabdominal infections and abscesses. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 747-754.)

KATSANDRI, A., AVLAMIS, A., PANTAZATOU, A., PETRICOS, L.G., LEGAKIS, N.J. & PAPAPARASKEVAS, J. 2006. In vitro activities of tigecycline against recently isolated Gram-negative anaerobic bacteria in Greece, including metronidazole resistant strains. *Diagnostic microbiology and infectious disease*, 55 (3):231-236.

KAYE, E.T. & KAYE, K.M. 2005. Fever and rash. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 108-116.)

KEUSCH, G.T. & KOPECKO, D.J. 2005. Shigelossis. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 902-906.)

KLUGMAN, K.P. 2003. Implications for antimicrobial prescribing of strategies based on bacterial eradication. *International journal of infectious diseases*, 7:S27-S31.

KNAPP, K.M. & ENGLISH, K.B. 2001. Carbapenems. *Seminars in infectious pediatric diseases*, 12(3):175-185.

KOCZURA, R. & KAZNOWSKI, A. 2003. Occurrence of Yersinia high-pathogenicity island and iron uptake systems in clinical isolates of *Klebsiella pneumoniae*. *Microbial pathogenesis*, 35:197-202.

KOLLEF, M.H. 2000. Inadequate antimicrobial treatment: an important determinant of outcome for hospitalised patients. *Clinical infectious diseases*, 31(Suppl 4):S131-S138.

LABARERE, J., STONE, R.A., OBROSKY, S., YEALY, D.M., MEEHAN, T.P., FINE, J.M., GRAFF, L.G., FINE, M.J. 2007. Comparison of outcomes for low-risk outpatients and inpatients with pneumonia: A propensity–adjusted analysis. *Chest*, 131(2):480-488.

LAGROU, K., VERHEIGE, N., JANSSENS, M., WAUTERS, G. & VERBIST, L. 1998. Prospective study of catalase-positive coryneform organisms in clinical specimens: Identification, clinical relevance and antibiotic susceptibility. *Diagnostic microbiology and infectious disease*, 30(1):7-15.

LAND, K.M. & JOHNSON, P.J. 1999. Molecular basis of metronidazole resistance in pathogenic bacteria and protozoa. *Drug resistance updates*, 2:289-294.

LANDRIGAN, C.P., ROTHSCHILD, J.M., CRONIN, J.W., KUSHAL, R., BURDICK, E., KATZ, J.T., LILLY, C.J., STONE, P.H., LOCKLEY, S.W., BATES, D.W. & CZEISLER, C.A. 2004. Effect of reducing work hours on serious medical errors in intensive care units. *New England journal of medicine,* 351:1838-1848.

LARI, A.R., HONAR, B.H. & ALAGHEHBANDAN, R. 1998. Pseudomonas infections in Tohid Burn Centre, Iran. *Burns*, 24:637-641.

LAWLEY, T.J. & YANCEY, K.B. 2005. Approach to the patient with skin disorder. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 283-288.)

LEE, T.H. 2005. Chest discomfort and palpitations. (*In* Kasper D.L., Brunwald E., Fausi A.S., Hauser S.L., Longo D.L., Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 76-81.)

LEIBOVICI, L., PAUL, M. & POZNANSKI, O. 1997. Mono therapy versus beta-lactam-aminoglycosides combination treatment for gram-negative bacteraemia: a prospective observational study. *Antimicrobial agents chemotherapy*, 41:1127-1133.

LEIBOVICI, L., SHRAGA, I., DRUCKER, M., KONIGSBERGER, H., SAMRA, Z. & PETLIK, S.D. 1998. The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection. *Journal of internal medicine*, 244:584-602.

LEMMEN, S.W., HAFNER, H., KOTERRICK, S., LUTTICKEN, R. & TOPPER, R. 2000. Influence of an infectious disease service on antibiotic prescription behaviour and selection of multi-resistant pathogens. *Infection*, 28(6):384-387.

LES **see** LESOTHO

LESOTHO. 1998. Nurses and Midwives Act. *Lesotho Government Gazette*, 49(1):103-116.

LESOTHO. Government of Lesotho (GOL) and Christian Health Association of Lesotho (CHAL). 2007. The memorandum of understanding between the Government of Lesotho and the Christian Health Association of Lesotho. Maseru. 13 p.

LESOTHO. HERA Consultancy. 2003. Interim report on Lesotho Pharmaceutical Sector: Review. Maseru. 80 p.

LESOTHO. HERA Consultancy. 2003. Final report on Lesotho Pharmaceutical Sector Review. Final Report, 2(6). Maseru. 9 p.

LESOTHO. Ministry of Health & Social Welfare. 2000. Health Sector Reforms plan. Maseru: Ministry of Health & Social Welfare. 82 p.

LESOTHO. Ministry of Health & Social Welfare. 2002. Health statistical tables. Maseru: Ministry of Health & Social Welfare. 161 p.

LESOTHO. Ministry of Health & Social Welfare. 2004. Lesotho demographic and health survey. Maseru: Ministry of Health & Social Welfare. 233 p.

LESOTHO. Ministry of Health & Social Welfare. 2006a. Essential medicines list. Maseru: Ministry of Health & Social Welfare. 131 p.

LESOTHO. Ministry of Health & Social Welfare. 2006b. Standard treatment guidelines. Maseru: Ministry of Health & Social Welfare. 173 p.

LESOTHO. National Health Training College (NHTC). 2004. Diploma in general nursing curriculum in Lesotho. Maseru: National Health Training College (NHTC). 185 p.

LESSER, C.F. & MILLER S.I. 2005. Salmonellosis. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 897-902.)

LI, X., 2005. Quinolone resistance in bacteria: emphasis on plasmid-mediated mechanisms. *International journal of antimicrobial agents*, 25:453-463.

LIGHT, R.W. 2005. Disorders of the pleura, mediastinum, diaphragm and chest wall. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 1565-1568.)

LIM, V.K.E., *chair.* s.a. Expert committee on rational use of antibiotics. http://www.acadmed.org.my/cpg/rational_use_of_antibiotics.htm. Date of access: 24 February 2006.

LOEB, M., BENTLEY, D.W., BRADLEY, S., CROSSLEY, K., GARIBALDI, R., GANTZ, N., McGEER, A., MUDER, R.R., MYLOTTE, J., NICOLLE, L.E., NURSE, B., PATON, S., SIMOR, A.E., SMITH, P. & STRAUSBAUGH, L. 2001. Development of minimum criteria for the initiation of antibiotics in residents of long-term-care facilities: results of a consensus conference. *Infection control and hospital epidemiology*, 22(2):120-124.

LOEB, M., SIMOR, A.E., LANDRY, L., WALTER, S., McARTHUR, M., DUFFY J., KWAN, D. & McGEER, A. 2001. Antibiotic use in Ontario facilities the provide chronic care. *Journal of general internal medicine*, 16:376-383.

LORENZE, J., BURCHER, T.R. & BOHUSLAVIZKI, K.H. 2001. Value of FDG PET in patients with fever of unknown origin. *Nuclear medicine communications*, 22(7):779-783.

LOWY, F.D. 2005. Staphylococcal Infections. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 814-823.)

LUZZARO, F., PERILLI, M., AMICOSANTE, G., LOMBARDI, G., BELLONI, R., ZOLLO, A., BIANCHI, C., TONIOLO, A. 2001. Properties of multi-resistant ESBL-producing *Proteus mirabilis* isolates and possible role of β-lactam/β-lactamase inhibitor combinations. *International journal of antimicrobial agents*, 17:131-135.

LYNCH, A.S. 2006. Efflux systems in bacterial pathogens: an opportunity for industrial intervention? An industry view. *Biochemical pharmacology*, 71:949-956.

MADAPPA, T., GO, C.H. 2009. Escherichia coli infections: emedicine infectious diseases. http://emedicine.medscape.com/article/217485-overview. Date of access: 21 April 2010

MACIULAITIS, R., JANUSONIS, T., PETRIKAITE, V.,AUKSTAKALNIENE, A. 2006. Assessment of antibiotic use and comparison with recommendation for their rational use. *Medicina (Kaunas),* 42 (12):999 – 1005.

MAKEDOU, K.G., TSIAKIRI, E.P., BISIKLIS, A.G., CHATZIDIMITRIOU, M., HALVANTZIS, A.A., NTOTSOU, K. & ALEXIOU-DANIEL, S. 2005. Changes in antibiotic resistance of the most common gram-negative bacteria isolated in intensive care units. *Journal of infection*, 60:245-248.

MAKOTA, M. 2006. Verbal communication with the M. Makota, Chief Laboratory Officer, Scott Hospital. (Notes of interview with the author.)

MALAYSIA. Health Technology Assessment Unit. 2002. Rational antibiotic utilisation in selected paediatric conditions. http://www.moh.gov.my/medical/HTA%20Report%20(PDP)/ Date of access: 1 March 2006.

MALCOLM, C. & MARRIE, J.L. 2003. Antibiotic therapy for ambulatory patients with community acquired pneumonia in an emergency department setting. *Archives of internal medicine,* 163:797-802.

MANGIONE-SMITH, R., McGLYN, E.A., ELLIOT, M.N., KROGSTAD, P. & BROOK, R.H. 1999. The relationship between perceived parental expectations and paediatrician antibiotic prescribing. *Pediatrics,* 103:711-718.

MARABE, Q.J. 1994. A study on the pattern of antibiotic prescription for in-patients at Queen Elizabeth II Hospital. Maseru: N.H.T.C. (Dissertation - Diploma in Pharmaceutical Technology.) 25 p.

MARCHESE, A., ARDITO, F., FADDA, G., FONTANA, R., LO CASCIO, G., NICOLETTI, G., SPECIALE, A.M. & SCHITO, G.C. 2005. The sentinel project: an update on the prevalence of antimicrobial resistance in community-acquired respiratory Streptococcus pneumoniae and Haemophilus spp in Italy. *International journal of antimicrobial agents*, 26:8-12.

MARERRO, A., MALLOORQUI-FERNADEZ, G., GUEVERA, T., GARCIA-CASTELLANOS, R. & GOMIS-RUTH, F.X. 2006. Unbound and acylated structures of the MecR1 extracellular antibiotic-sensor domain provide insights into signal-transduction system that triggers methicillin resistance. *Journal of molecular biology,* 361:506-521.

MARRIE, T.L., CAMBELL, D.G., WALKER, D.H. & LOW, D.E. 2005. Pneumonia. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 1528-1540.)

MARTIN, J.N., ROSE, D.A., HADLEY, W.K., PERDREAU-REMINGTON, F., LAM, P.K. & GERBERDING, J.L. 1999. Emergence of trimethoprim-sulfamethoxazole resistance in the AIDS Era. *Journal of infectious diseases*, 180:1809-1818.

MBO-BUDIAKI, L. K. 2010. Verbal communication with Mbo-Budiaki, Principal Laboratory Technologist at Queen II Hospital. (Notes of interview with the author.)

MARTINEZ, M., INGLADA, L., OCHOA, C., VILLAGRASA, J. 2007. Assessment of antibiotic prescription in acute urinary tract infectionin adults. *Journal of infection*, 4(3):235-244

McCALL, C.O. & LAWLEY, T.J. 2005. Eczema, psoriasis, cutaneous infections, acne, and other common skin disorders. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 288-296.)

McCORMACK, J.P. & BROWN, G. 2008. Traumatic skin and soft tissue infections. (*In* Koda-Kimble, M.A., Young, L.Y., Alldredge, B.K., Corelli, R.L., Guglielmo, B.J., Kradjan,

W.A. & Williams, B.R., *eds.* Applied therapeutics: the clinical use of drugs. 9th ed. Philadelphia, Pa.: Wolters Kluwer Health/Lippincott & Wilkins. p. 67-1 - 67-10.)

McFADDEN, E.R., Jr. 2005. Asthma. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 1508-1516.)

McNULTY, C.A.M., KANE, A., FOY, C.J.W., SYKES, J., SAUNDERS, P. & CARTWRIGHT, K.A.V. 2000. Primary care workshops can reduce and rationalize antibiotic prescribing. *Journal of antimicrobial chemotherapy*, 46:493-499.

MELLANO, R.G., DAVIDSON, R.J., MUSGRAVE, H.L. & FORWARD, K.R. 2006. Cephalosporin resistance in Klebsiella pneumoniae from Nova Scotia, Canada. *Diagnostic microbiology and infectious disease*, 56:197-205.

MERMEL, L.A., FARR, B.M., SHERERTZ, R.J., RAAD, I.I., O'GRADY, N., HARRIS, J.S. & CRAVEN, D.E. 2001. Guidelines for the management of intravascular catheter-related infections. *Clinical infectious disease*, 23:1249-1272.

MILLS-ROBERTSON, F., ADDY, M.E., MENSAH, P. & CRUPPER, S.S. 2002. Molecular characterization of antibiotic resistance in clinical salmonella typhi isolated in Ghana. *FMES Microbiology letters*, 215(2):249-253, October.

MINGEOT-LECLERCQ, M., GLUPCZYNSKI, Y. & TULKENS, P.M. 1999. Aminoglycosides: activity and resistance. *Antimicrobial agents and chemotherapy*, 43(4):727-737.

MINGEOT-LECLERCQ, M. & TULKENS, P.M. 1999. Aminoglycosides: Nephrotoxicity. *Antimicrobial agents and chemotherapy*, 43(5):1003-1012.

MINISTRY OF HEALTH **see** SINGAPORE. Ministry of Health

MINISTRY OF HEALTH & SOCIAL WELFARE **see** LESOTHO. Ministry of Health & Social Welfare

MOSER, C.A. & KALTON, G. 1993. Survey methods in social investigation. 2nd ed. Aldershot: Dartmouth Publishing Company. 555 p.

MOURAD, O., PALDA, V. & DETSKY, A.S. 2003. A comprehensive evidence-based approach to fever of unknown origin. *Archives of internal medicine*, 163:545-551.

MUNFORD, R.S. 2005. Severe sepsis and septic shock. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds*. Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 1606-1612.)

MURPHY, T.F. 2005. Haemophilus infections. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds*. Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 864-867.)

MUSHER, D.M. 2005. Pneumococcal infections. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds*. Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 806-814.)

MUSHTAQ, S., GE, Y. & LIVERMORE, D.M. 2004. Doripenem versus *Pseudomonas aeruginosa* in vitro: activity against isolates, mutants, and transconjugants and resistance selection potential. *Antimicrobial agents and chemotherapy*, 48(8):3086-3092.

NATHWANI, D., RUBINSTEIN, E., BARLOW, G. & DAVEY, P. 2001. Do guidelines for community-acquired pneumonia improve the cost effectiveness of hospital care? *Clinical infectious diseases*, 32:728-741.

NATHWANI, D.L. & DAVEY, P. 1999. Antibiotic prescribing - are there lessons for physicians. *QJM: an international journal of medicine*, 12(5):287-292.

NATIONAL HEALTH TRAINING COLLEGE (NHTC) **see** LESOTHO. National Health Training College (NHTC)

NATIONAL UNIVERSITY OF LESOTHO (NUL). 2003. Curriculum for bachelor of science in nursing. Maseru. 105 p.

NEUMAN, W.L. 2006. Social research methods. 6th ed. Boston, Mass.: Pearson Education. 534 p.

NGUYEN, M. & CHUNG, E.P. 2005. Telithromycin: the first Ketolide antimicrobial. *Clinical therapeutics,* 27(8):1144-1163.

NHTC **see** NATIONAL HEALTH TRAINING COLLEGE

NICKLIN, J., GRAEME-COOK, K., KILLINGTON R. 2002. Instant notes: Microbiology. 2nd ed. Oxford: BIOS Scientific Publishers Ltd. 330 p.

NIEDERMAN, M.S. 2005. Principles of appropriate antibiotic use. *International journal of antimicrobial agents*, 23(Suppl. 3):S170-S175.

NILIUS, A.M. & MA, Z. 2002. Ketolides: the future of the macrolides? *Current opinion in pharmacology*, 2:1-8.

NTHOLI, M. 2009. Verbal communication with M. Ntholi, Executive Secretary of Chal. (Notes of interview with the author.)

NUL **see** NATIONAL UNIVERSITY OF LESOTHO

OHL, C.A. & POLLACK, M. 2005. Infections due to Pseudomonas species and related organisms. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds*. Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 889-897.)

ONE WORLD-NATIONS ONLINE. s.a. Least developed countries. http://www.nationsonline.org/oneworld/least_developed_countires.htm. Date of access: 7 April 2006.

OSMON, D.R. 2000. Antimicrobial prophylaxis in adults. *Mayo Clinic proceedings*, 75:98-109.

ONWUAMAEGBU, M.E., BELCHER, R.A. & SOARE, C. 2005. A review of the clinical significance of atypical bacteria. *Journal of international medical research*, 33:1-20.

PANIGRAHI, D., ROTIMI, V.O., DHAR, R., CHUGH, T.D., DHAR, P.M., GHALI, A., SAAD, A., SANYAL, S.C. & VARGHESE, T.L. 2001. Anaerobic bacterial flora of intra-abdominal infections and their antimicrobial susceptibility pattern in Kuwait. *Anaerobe*, 7:291-295.

PARSONNET, J. & MAGUIRE, J.H. 2005. Osteomyelitis. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds*. Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 745-749.)

PEREZ, F., ENDIMIANI, A., HUJER, K.M. & BONOMO, R.A. 2007. The continuing challenge of ESBLs. *Current opinion in pharmacology*, 7:459-469.

PETRI, W.A., Jr. 2001. Penicillins, cephalosporins and other β-lactam antibiotics. (*In* Hardman, J.G. & Limbird, L.E., *eds*. The pharmacological basis of therapeutics. 10th ed. New York: McGraw-Hill. p. 1189-1215.)

PHALIMA, M. 2003. A study of the sources of commonly isolated bacteria pathogens and their sensitivity patterns to commonly prescribed antibiotics at Queen Elizabeth II Hospital. Maseru: N.H.T.C. (Dissertation - Diploma in Pharmaceutical Technology.) 34 p.

PIER, G.B. 2005. Molecular mechanisms of microbial pathogenesis. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds*. Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 700-706.)

PINDER, M., BELLOMO, R. LIPMAN, J. 2002. Pharmacological principles of antibiotic prescription in the critically ill. *Anaesthesia and intensive care*, 30(2):134-144.

POLK, H.C., Jr. & CHRISTMAS, A.B. 2000. Prophylactic antibiotics in surgery and surgical wound infections. *American surgeon,* 66(2):105-111.

POPA, R.I., GRAY, L.A. & KALLMES, D.F. 2009. Urinary tract infections in the potential vertevroplasty patient: incidence, significance and management. *American journal of neuroradiology,* 30:227-231.

QUEEN II HOSPITAL. Department of Pharmacy. 2002. Drug consumption electronic data base, 1999-2002. Maseru: Queen II Hospital. Department of Pharmacy.

QURAH, S., CUNHA, B., DUA, P., LESSNAU K.D., 2009. Pseudomonas infections: emedicine infectious diseases. http://emedicine.medscape.com/article/217485-overview. Date of access: 21 April 2010

RAITHULE, M. 2010. Verbal communication with Raithule, Laboratory Technician-in-charge, Berea Hospital. (Notes of interview with the author.)

RAM, S. & RICE, P.A. 2005. Gonococcal infections. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 855-862.)

RAVIGLIONE, M.R. & O'BRIEN, R.J. 2005. Gonococcal infections. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 953-966.)

RAYMONT, A., LAY-YEE, R., PEARSON, J. & DAVIS, P. 2005. New Zealand general practitioners characteristics and workload: the national primary medical care survey. *Journal of the New Zealand Medical Association,* 118(1215). 9 p. http://www.nzma.org.nz/journal/118-1215/1475/ Date of access: 18 April 2009.

REES, R.E. & BETTS, R.F. 1996. Antibiotic use. (*In* Rees, R.E. & Betts R.F., *eds.* A practical approach to infectious diseases. Boston, Mass.: Little, Brown. p. 1059-1097.)

REILLY, J.J., Jr., SILVERMAN, E.K. & SHAPIRO, S.D. 2005. Chronic obstructive airways disease. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 1547-1554.)

ROLAIN, J.M., BROUQUI, P., KOECHLER, J.E., MAGUINA, C., DOLAN, M.J. & RAOULT, D. 2004. Recommendations for treatment of human infections caused by Bartonella species. *Antimicrobial agents and chemotherapy*, 48(6):1921-1933.

RONALD, A. 2002. The etiology of urinary tract infections: traditional and emerging pathogens. *American journal of medicine*, 113(1):14-19, 8 July.

ROOS, L.R. & TYLER, K.L. 2005. Meningitis, encephalitis, brain abscess, and empyema. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 2371-2404.)

RUBIN, M.A., GONZALES, R. & SANDE, M.A. 2005. Infections of the upper respiratory tract. (*In* Kasper D.L., Brunwald E., Fausi A.S., Hauser S.L., Longo D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 185-193.)

RUSSO, T.A. 2005. Diseases caused by gram-negative bacteria. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 878-885.)

SABELLA, C. & GOLFARB, J. 1999. Principles of selection of and use of antimicrobial agents. *Seminars in pediatric infectious disease*, 10(1):3-13.

SAHA, S.K., BAQUI, A.H., DARMSTADT, G.L., RUHULAMIN, M., HANIF, M., ARIFEEN, S.E., OISHI, H., SANTOSSHAM, M., NAGATAKE, T. & BLACK, R.E. 2005. Invasive *Haemophilus influenzae* type b diseases in Bangladesh, with increased resistance to antibiotics. *Journal of paediatrics*, 146(2):227-233, February.

SATO, Y., KANEKO, K. & INOUE, M. 2007. Macrolide antibiotics promote the LPS-induced up-regulation of prostaglandin E receptor EP_2 and thus attenuate macrolide suppression of IL-6 production. *Prostaglandins, leukotrienes and essential fatty acids*, 76:181-188.

SCHACHT, J. 1999. Antioxidant therapy attenuates aminoglycoside-induced hearing loss. *Annals of New York Academy of Sciences*, 884:125-130.

SCHAEFER, A.J. 2003. The expanding role of fluoroquinolones. *Disease-a-month*, 49:129-147.

SCOTTISH INFECTIONS STANDARDS AND STRATEGIES GROUP. 2003. Occasional communications: good practice guidance for antibiotic prescribing. *Journal of Royal College of Physicians Edinburgh,* 33:281-284.

SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK (SIGN). 2008. Antibiotic prophylaxis in surgery: a national clinical guideline. Edinburgh. (SIGN Publication, 104:1-70.)

SHA, S.H. & SCHACHT, J. 1999. Salicylate attenuates gentamicin-induced ototoxicity. *Laboratory investigation*, 79(7):807-813.

SHANKAR, N., LOCKATELL, V.C., BAGHDAYAN, A.S., DRAKENBERG, C., GILMORE, M.S. & JOHNSON, D.E. 2001. Role of Enterococcus faecalis surface protein Esp in the pathogenesis of ascending urinary tract infection. *Infection and immunity*, 69(7):4366-4372.

SHORTRIDGE, D., RAMER N., DARWISH, A. & FLAMIN, R.K. 1999. Activity of the ketolide ABT-773 as measured by broth microdilution against macrolide-susceptible and resistant Streptococcus spp. *Clinical microbiology of infections*, 5(Supplement 3):132.

SIGN **see** SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK

SILEN, W. 2005a. Abdominal pain. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 82-84.)

SILEN, W. 2005b. Acute appendicitis and peritonitis. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 1805-1808.)

SINGAPORE. Ministry of Health. 2000. Use of antibiotics in adults: clinical practice guidelines. http://www.moh.gov.sg/corp/publications/topicby.do? Date of access: 1 March 2006.

SINGH, N., ROGERS, P., ATWOOD, C.W., WAGENER, M.M. & YU, V.L. 2000. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive case unit: a proposed solution for indiscriminate antibiotic prescription. *American journal of respiratory critical care medicine,* 162:505-511.

SIRINAVIN, S., GARMER, P. 1999. Antibiotic for treating salmonella gut infections. *Cochrane database of systematic reviews*, 1: Art. No.: CD001167.

SLINGER, R., CHAN, F., FERRIS, W., YEUNG, S., ST. DENIS, M., GABOUR, I. & ARON, S.D. 2006. Multiple combination antibiotic susceptibility testing of nontypable *Haemophilus influenzae* biofilms. *Diagnostic microbiology and infectious disease*, 56:247-253.

SOHAIL, M.R., KHAN, A.H., HOLMES, D.R., Jr., WILSON, W.R., STECKELBERG, J.M. & BADDOUR, L.M. 2005. Infectious complications of percutaneuos vascular closure devices. *Mayo Clinic proceedings*, 80(8):1011-1015.

SPEELMAN, P. 2005. Leptospirosis. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds*. Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 988-991.)

SPEIZER, F.E. 2005. Environmental lung diseases. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds*. Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 1521-1522.)

STAMM, W.E. 2002. Scientific and clinical challenges in the management of urinary tract infections. *American journal of medicine*, 113(1A):1S-4S, July.

STAMM, W.E. 2005. Urinary tract infections and pyelonephritis. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds*. Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 1715-1721.)

STATHI, M., AVGERINOU, H., MIRIAGOU, V., FLEMETAKIS A., DANIILIDOU, M., KYRIAKIS, K., TZELEPI, E. 2007. Antimicrobial susceptibility of *Neisseria gonorrhoea* isolated in Greece in 2005: Dramatic increase in quinolone resistance rate due to a single serovar. *Journal of antimicrobial chemotherapy agents,* 29: S303 – S306.

STATISTICAL ANALYSIS SYSTEMS® FOR WINDOWS 9.1®®. 2005. SAS Institute Inc., 2002-2003.

STEINBERG, I. 2008. Principles of infectious diseases. (*In* Koda-Kimble, M.A., Young, L.Y., Alldredge, B.K., Corelli, R.L., Guglielmo, B.J., Kradjan, W.A. & Williams, B.R., *eds*. Applied therapeutics: the clinical use of drugs. 9th ed. Philadelphia, Pa.: Wolters Kluwer Health/Lippincott & Wilkins. p. 96-1 - 96-19.)

STEINMAN, M.A., LANDEFELD, C.S. & GONZALES, R. 2003. Predictors of broad spectrum antibiotic prescribing for acute respiratory tract infection in adult primary care. *Journal of American Medical Association*, 289(6):719-725.

STEVENS, D.L. 2005. Infections of the skin, muscle, and soft tissues. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 740-745.)

STEVENS, D.L., BISNO, A.L., CHAMBERS, H.F., EVERETTE, E.D., DELINGER, P., GOLDSTEIN, E.J.C., GORBACH, S.L., HIRSCHMANN, J.V., KAPLAN, E.L., MONTOYA, J.G. & WADE, J.C. 2005. IDSA guidelines. Practice guidelines for the diagnosis and management of skin and soft tissue infections. *Clinical infectious disease,* 41:1373-1406.

STEVENS, D.L. & BRYANT, A.E. 2002. The role of clostridial toxins in the pathogenesis of gas gangrene. *Clinical infectious diseases*, 35:S93.

STEPHENS, D.S., MUNFORD, R.S. & WETZLER, L.M. 2005. Meningococcal infections. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 849-855.)

STEYN, H.S. 2009. Manual for the determination of effect size indices and practical significance. http://www.puk.ac.za/opencms/export/PUK/html/fakulteite/natuur/skd/handleiding_e.html 1-1:8-25. Date of access: 26 August 2009.

STRUBLE, K., BRONZE, M.S. JACKSON, R.L.,GONZALEZ G. 2009. Proteus infections: emedicine infectious diseases. http://emedicine.medscape.com/article/226434-overview. Date of access: 21April 2010

SWARTZ, M.N. 2004. Bacterial meningitis - a view of the past 90 years. *New England journal of medicine*, 351(18):1826-1828.

SZYCH, J., CIELIK, A., PACIOREK, J., KAUEWSKI, S. 2001. Antibiotic resistance in Salmonella enterica subsp. Entericadstrains isolted in Poland from 1998 to 1999. *International journal of antimicrobial agents*, 18(1):37-42

TALAN, D.A., CITRON, D.M., ABRAHAMIAN, F.M., MORGAN, G.J., GOLGSTEIN, E.J.C. 1999. Bacteriologic analysis of infected dog and cat bites. *The New England journal of medicine*, 340(2):85-92.

TAN, M., MAHAJAN-MIKLOS, S. & AUSUBEL, F.M. 1999. Killing of Caenorhaditis elegans by *Pseudomonas aeruginosa* used to model mammalian bacterial pathogenesis. *Proceedings of National Academy of Sciences*, 96:715-720.

TENOVER, F.C. 2006. Mechanisms of antimicrobial resistance in bacteria. *American journal of infection control*, 34(5):S3-S10.

THOMPSON, R.L. & WRIGHT, A.J. 1998. General principles of antimicrobial therapy. *Mayo Clinic proceedings*, 73:995-1006.

THUONG, M., SHORTGEN, F., ZAZEMPA, V., GIROU, E., SOUSSY, C.J. & BUISON-BRUN, C. 2000. Appropriate use of restricted antimicrobial agents in hospitals: the importance of empirical therapy and assisted re-evaluation. *Journal of antimicrobial chemotherapy*, 46:501-508.

TIMURKAYNAK, F., CAN, F. & AZAB, K.O., DEMIRBILEK, M., ARSLAN, H. & KARAMAN, S.O. 2006. In vitro activities of non traditional antimicrobials alone or in combination against multidrug-resistant strains pseudomonas aeruginosa and *Acinebacter baumanni* isolated from intensive care units. *International journal of antimicrobials agents*, 27:224-228.

TLALI, R. 2001. A study to determine the rational behind common cold treatment at Queen Elizabeth II Hospital. Maseru: N.H.T.C. (Dissertation - Diploma in Pharmaceutical Technology.) 19 p.

TODAR, K. 2009. Mechanisms of bacterial pathogenesis. Todar's online textbook of bacteriology. On-line book, p. 1-8. http://www.textbookofbacteriology.net/pathogenesis_2.html Date of access: 18 December 2009.

TOWSEND, R. & RIDGWAY, E.J. 2005. Rational use of antibiotics in surgery. *Surgery*, 23(8):293-296.

TRACY, J.W. & WEBSTER, L.T., Jr. 2000. Drugs used in chemotherapy of protozoal infections. (*In* Hardman, J.G. & Limbird, L.E., *eds.* The pharmacological basis of therapeutics. 10th ed. New York: McGraw-Hill. p. 1097-1117.)

TRAP, B. & HANSEN, E.H. 2002. Cotrimoxazole prescribing by dispensing and non dispensing doctors: do they differ in rationality? *Tropical Medicine and International Health,* 7(10):878-885.

TSAKAHARA, M., TSUNEOKA, H., IINO, H., MARAMO, I., TAKAHASHI, H. & UCHIDA, M. 2000. Bartonella henselae infection as a cause of fever of unknown origin. *Journal of clinical microbiology*, 38(5):1990-1991.

TSAY, R.W., SIU, L.K., FUNG, C.P., CHANG, F.Y. 2002. Characteristics of bacteremia between community-acquired and nosocomial *Klebsiella pneumoniae* infection. *Archives of internal medicine*, 162:1021-1027

TSIKOANE, G.L.. 2009. Verbal communications with the head of Patient Billing Section of the Queen II and Scott Hospitals. (Notes of interview in possession of the author.)

TURNER, L.K. & KNIGHTON, D. 1989. Advanced mathematics. 2nd ed. Essex: Longman Group.

TZANAKAKI, G. & MASTRANTONIO, P. 2007. Aetiology of bacterial meningitis and resistance to antibiotics of causative pathogens in Europe and the in the Mediterranean region. *International journal of antimicrobial agents,* 29:621-629.

ULGER, T.N., CELIK, C., CAKICI, O. & SOYLETIR, G. 2004. Antimicrobial susceptibilities of *Bacteroides fragilis* and *Bacteroides thetaiotaomicron* strains isolated from clinical specimens and human intestinal microbionta. *Anaerobe*, 10:255-259.

UNITED NATIONS. 2003. The United Nations common country assessment report on Lesotho. Health situation analysis. 72 p.

UNKMEIR, A., SCHMIDT, H. 2000. Structural analysis of phage borne *stx* genes and flanking sequences in shiga toxin producing Escherichia coli and Shigella dysenteriae Type I strains. *Infection and immunity*, 68(9):4846-4864.

UMEH, O., BERKOWITZ B. 2009. Klebsiella infections: emedicine infectious diseases. http://emedicine.medscape.com/article/9907211-overview. Date of access: 21April 2010

UTTS, J.M. & HECKARD, R.F. 2007. Mind on statistics. 3rd ed. Duxbury: Thompson Brookes/Cole. 770 p.

VAKULENCO, S.B. & MOBASHERY, S. 2003. Versatility of aminoglycosides and prospects for their future. *Clinical microbiology reviews*, 16(3):430-450.

VALLE, J.D. 2005. Peptic ulcer disease and related disorders. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 1746-1762.)

VAN DE BEEK, D., DE GANS, J., SPANJAARD, L., VERMEULEN, M. & DANKERT, J. 2002. Antibiotic guidelines and antibiotic use in adult bacterial meningitis in the Netherlands. *Journal of antimicrobial chemotherapy,* 49:661-666.

VAN LOON, H.J., VRIENS, M.R., FLUIT, A.C., TROELSTRA, A., VAN DER WERKEN, C., VERHOEF, J. & BONTEN, M.J.M. 2004. Antibiotic rotation and development of g-negative antibiotic resistance. *American journal of respiratory critical care medicine,* 171:480-481.

VERA-CABRERA, L., GOMEZ-FLORES, A., ESCALANTE-FUENTES, W.G. & WELCH, O. 2001. In vitro activity of PNU-100766 (Linezolid), a new xazolidinone antimicrobial, against *Nocardia brasiliensis*. *Antimicrobial agents and chemotherapy*, 45(12):3629-3630.

WALZER, P.D. 2005. Pneumocystis infection. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 1194-1196.)

WANING, B. & MONTAGNE, M. 2001. Pharmacoepidemiology: principles and practice. New York: McGraw-Hill. 209 p.

WATERA ,C., TODD, J., MUWENGE, R., WHITWORTH, J., NAKIYINGI-MITRO, J., BRINK, A., MIIRO, G., ANTVELINK, L., KAMALI, A., FRENCH, N. & MERMIN, J. 2006. Feasibility and effectiveness of cotrimoxazole prophylaxis for HIV/AIDS-1 infected adults attending and HIV/AIDS clinic in Uganda. *Journal of acquired immune deficiency syndrome,* 42(3):373-378.

WEINBERGER, S.E. 2005. Cough and haemoptysis. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 205-208.)

WEINSTEIN, P., TOWNS, M.L. & QUARTEY, S.M. 1997. The clinical significance of positive blood cultures in the 1990s:a prospective comprehensive evaluation of the microbiology, epidemiology and outcome of bacteraemia and fungemia in adults. *Clinical infectious disease,* 24:584-602.

WELLER, T.M.A. & JAMIESON, C.E. 2004. The expanding role of the antibiotic pharmacist. *Journal of antimicrobial chemotherapy*, 54:295-298.

WELLER, P.F. 2005. Protozoal intestinal infections and trichomoniasis. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 1248-1252.)

WESSELS, M.R. 2005. Streptococcal and enterococcal infections. (*In* Kasper, D.L., Brunwald, E., Fausi, A.S., Hauser, S.L., Longo, D.L. & Jameson, J.L., *eds.* Harrison's Principles of Internal Medicine. New York: McGraw-Hill. p. 823-831.)

WILCOX, M.H. 2003. Clostridium difficile infection and pseudomembranous colitis. *Best practice & research clinical gastroenterology*, 17(3):475-493.

WILLIAMS, J.D. 2001. Evaluation of the safety of macrolides. *International journal of antimicrobial agents*, 18:S79.

WILSON, J.W., SCHURR, M.J., LEBLANC, C.L., RAMAMURTHY, R., BUCHANAN, K.L., NICKERSON, C.A. 2002. Mechanisms of bacterial pathogenicity. *Postgraduate medical journal,* 78: 216-224.

WILTON, P., SMITH, R., COAST, J. & MILLAR, M. 2002. Strategies to contain the emergence of antimicrobial resistance: a systematic review of effectiveness and cost - effectiveness. *Journal of health services research and policy*, 7(2):111-117.

WONG, C.S., JELACIC, S., HABEEB, R.L., WATKINS, S.L. & TARR, P.L. 2000. The risk of haemolytic-uraemic syndrome after antibiotic treatment of Escherichia col. *New England journal of medicine*, 342:1930-1936.

WORLD BANK. 2008. World development indicators database: World bank list of economies. http://siteresources.worldbank.org/Datastatistics/Resources/CLAS.xls Date of access: 20 March 2009.

WORLD HEALTH ORGANIZATION. 2001. WHO global strategy for containment of antimicrobial resistance. p. 1- 81. http://www.who.int/drugresistance/WHO_Global_Strategy English.pdf. Date of access: 01 April 2010.

WRIGHT, G.D. 2005. Bacterial resistance to antibiotics: enzymatic degradation and modification. *Advanced drug delivery and reviews*, 57:1451-1470.

ZACHARIAH, R., HARRIES, A.D., NKHOMA, W., ARENDT, V., NCHINGULA, D., CHANTULO, A. 2002. Behavioural characteristics, prevalence of Chlamydia trachomatis and antibiotic susceptibility of Neisseria gonorrhoea in men with urethral discharge in Thyolo, Malawi. *Transactions of the royal society of tropical medicine and hygiene*, 96 (3): 232-235.

ZAFAR, A., HUSSAIN, Z., LOMAMA, E., SIBILLIE, S., IRFAN, S. & KHAN, E. 2008. Antibiotic susceptibility of pathogens isolated from patients with community acquired respiratory tract infections in Pakistan - the active study. *Journal of Ayub medical college of Abbottabad*, 20(1):1-9.

ZGURSKAYA, H. & NIKAIDO, H. 2000. Multidrug resistance mechanisms: efflux across two membranes. *Molecular microbiology*, 37:219-225.

ZHAO, S., WHITE, D.G., GE, B., AYERS, S., FRIEDMAN, S., ENGLISH, L., WAGNER, D., GAINES, S. & MENG, J. 2001. Identification and characterization of integrin-mediated antibiotic resistance among shiga toxin- producing *Escherichia coli* isolates. *Applied and environmental microbiology*, 67(4):1558-1564.

ZHONG, P. & SHORTRIDGE, V.D. 2000. The role of efflux in macrolide resistance. *Drug resistance updates*, 3:325-329.

APPENDICES

Appendix 1

Data collection tool -1: Individual in-patient data collection sheet.

Study Site: _____ Month & Year_____ Dates of Start and End of data Collection: Start _____ End _____ Ward _____ Ward Type: Surgical/Medical? _____

PATIENT PARTICULARS: Patient Code _____ Age_____ Sex _____

Antibiotic treatment started on_____ Antibiotic treatment stopped on _____Status on Antibiotic stoppage: Improved ☐ Not improved ☐ Died ☐

SYMPTOMS :i _____ii._____iii._____iv._____ **DIAGNOSIS**_____

Infection hallmark i._____ ii._____ **SITE OF INFECTION:** _____

GRAMS STAIN PERFORMED AND BACTERIAL MORPHOLOGICAL CHARACTERISTICS IDENTIFIED BEFORE ANTIBIOTIC THERAPY INITIATION?:
Yes ☐ No ☐ If yes, **Specimen** _____ **Results**: Gram +ve cocci ☐ Gram –ve bacilli ☐ Organisms unidentified ☐

Possible target organisms for antibiotic Therapy: _____
CULTURE SENSITIVITY TEST PERFORMED (CST)? Yes ☐ No ☐ If yes, **Date** _____ **Results**: Pathogens sensitive to: _____

_____, Pathogens Resistant to: _____

PRESCRIBED ANTIBIOTIC/ANTIBIOTICS

Name of Antibiotic	B/f CST or After CST	Dose	Date Started	Date Stopped	Discharged on for _____ days	Side-effects noted

PATIENT'S TREATMENT RESPONSE MONITORING: Monitoring Parameter: _____ Subjective ☐ Objective ☐

Date													
Data													

Appendix 2

Data collection tool -2: Individual out-patient data collection sheet.

Study Site: _____ Month & Year_____ Dates of Start and End of data Collection: Start _____ End _____

PATIENT PARTICULARS: Patient Code _____ Age_____ Sex _____

PH/SYMPTOMS :i _____ ii._____ iii._____ iv._____ **DIAGNOSIS**_____

Infection hallmark i._____ ii._____ **SITE OF INFECTION:** _____

GRAMS STAIN PERFORMED AND BACTERIAL MORPHOLOGICAL CHARACTERISTICS IDENTIFIED BEFORE ANTIBIOTIC THERAPY INITIATION?:
Yes ☐ No ☐ If yes, **Specimen** _____ **Results**: Gram +ve cocci ☐ Gram –ve bacilli ☐ Organisms unidentified ☐

Possible target organisms for antibiotic Therapy: _____

CULTURE SENSITIVITY TEST PERFORMED? Yes ☐ No ☐ If yes, **Date** _____ **Results**: Pathogens sensitive to: _____

_____, Pathogens Resistant to: _____

PRESCRIBED ANTIBIOTIC/ANTIBIOTICS: Prescriber's Qualification – Doctor ☐ **Nurse Clinician** ☐

Name of Antibiotic	Dose	Date Started	No of days Prescribed for	Dispenser's comments				
				Prescriber's Choice			Availability	
				1st	2nd	3rd	Available	Not available

Appendix 3

Data collection tool: 3 Antibiotic prescription Data Summary tool for prescription rationality rating -Inpatients

Rec No.	Criteria for determining appropriateness of antibiotic prescription																
	Establishing need for antibiotic prescription						Determining of appropriateness of antibiotic prescriptions										
	Criteria 1	Criteria 2	Criteria 3	Criteria 4	Criteria 5		Criteria 6	Criteria 7	Criteria8	Criteria 9	Criteria 10	Criteria11	Criteria 12	Criteria 13	Criteria 14	Criteria15	Criteria 16
	Suggestive signs or symptoms of infection indicated in case notes?	Suggestive signs or symptoms of infection absolute for bacterial infection?	Site of infection or possible site for infection identified?	Potential source of infection e.g. indwelling catheter & prosthetic devices surgical & other open wounds present?	5(i) Presence of infection established by objective data	5(ii) Presence of infection inferred from symptoms only?	Antibiotic prescribed alone?	Initial antibiotic treatment modified by addition of other antibiotics to regimen?	Initial antibiotic treatment modified by substitution of any antibiotics in regimen?	Prescribed doses of antibiotic or antibiotics correct?	Antibiotics in multiple therapy compatible ?	Spectra of activity of 2 or more antibiotics in multiple antibiotic therapy similar?	Prescribed antibiotic or antibiotics indicated against all possible pathogens associated with site or source of infection?	Bacterial morphological & Grams stain characteristics determined before therapy initiation?	CST ordered before antibiotic therapy initiation?	CST performed for antibiotic therapy evaluation or before therapy modification?	Antibiotic choice based on CST results?

Appendix 4

Data collection tool: 4 Antibiotic prescription Data Summary tool for prescription rationality rating - Outpatients

Rec #	Criteria for characterising the pattern and appropriateness of antibiotic prescriptions															Prescribers Antibiotic choice category	Antibiotic choice preference determined by drug availability?
	Establishing need for antibiotic prescription						Determining appropriateness of prescribed antibiotic/antibiotics										
	Criteria 1	Criteria 2	Criteria 3	Criteria 4	Criteria 5	Criteria 6	Criteria7	Criteria 8	Criteria 9	Criteria 10	Criteria 11	Criteria12	Criteria 13	Criteria 14	Criteria 15		
	Suggestive signs or symptoms of infection indicated in case notes?	Suggestive signs or symptoms of infection absolute for bacterial infection?	Site of infection or possible site for infection identified?	Potential source of infection e.g. indwelling catheter & prosthetic devices surgical & other open wounds present?	Presence of infection established by objective data?	Presence of infection inferred from symptoms only?	Antibiotic prescribed alone?	Prescribed doses of antibiotic or antibiotics correct?	Antibiotics in multiple therapy compatible ?	Spectra of activity of 2 or more antibiotics in multiple antibiotic therapy similar?	Prescribed antibiotic or antibiotics indicated against all possible pathogens associated with site or source of infection?	Bacterial morphological & Grams stain characteristics determined before therapy initiation?	CST performed before initiation of or during antibiotic therapy?	Antibiotic choice based on CST results?			

Appendix 5

Examples of antibiotic prescriptions classified into categories of appropriateness according to employed method of assessment.

Prescription Record number	Prescription category	Notation on prescription conformity to applicable criteria		Diagnosis/ Symptom(s)	Prescribed antibiotic(s)
		YES: Prescription conformed to indicated criteria (Criteria number in parenthesis)	NO: Prescription did not conform to indicated criteria (Criteria number in parenthesis)		
123 (Motebang - 60)	A1 (Outpatient)	– (1) Sign and symptom present – (2) Sign and symptom absolute for bacterial infection – (3) Site of infection identified – (6) Presence of infection inferred from symptoms only – (7) Antibiotic prescribed alone – (8) Dose correct – (11) Prescribed antibiotic indicated against possible pathogens	– (4) Potential source of infection present – (5) Presence of infection established by objective data	Cough, fever, shortness of breath	Erythromycin
16 (Queen II - 15	A1 (Inpatient)	– (1) Sign and symptom present – (2) Sign and symptom absolute for bacterial infection – (3) Site of infection identified – (6)Presence of infection inferred from symptoms only – (10) Prescribed doses of antibiotics correct – (11) Antibiotics in multiple therapy compatible – (13) Prescribed antibiotic(s) indicated against most possible pathogens associated with infection –	– (4) Potential source of infection present – (5) Presence of infection established by objective data – (7) Antibiotic prescribed alone – (8) Initial antibiotic therapy modified by addition of other antibiotics – (9) Initial antibiotic therapy modified by addition of other antibiotics – (12)Spectra of 2 or more antibiotic in multiple therapy similar – (14)Bacterial morphological and Grams-stain done before therapy initiation – (15) Culture sensitivity test ordered before antibiotic therapy initiation – (16)Culture sensitivity test performed in the course of antibiotic therapy – (17)Antibiotic based on culture sensitivity test results	Genital septic ulcer	Cloxacillin Metronidazole
2 (Maluti-304)	A2 (Outpatient)	– (1) Sign and symptom present – (3) Site of infection identified	– (2) Sign and symptom absolute – (4) Potential source of infection present	Bronchitis	Erythromycin

Prescription Record number	Prescription category	Notation on prescription conformity to applicable criteria		Diagnosis/ Symptom(s)	Prescribed antibiotic(s)
		YES: Prescription conformed to indicated criteria (Criteria number in parenthesis)	**NO: Prescription did not conform to indicated criteria (Criteria number in parenthesis)**		
		– (6)Presence of infection inferred from symptoms only – (7) Antibiotic prescribed alone – (11) Prescribed antibiotic indicated against possible pathogens – (13) Prescribed antibiotic(s) indicated against most possible pathogens associated with infection	– (5) Presence of infection established by objective data		
24 (Queen II - 23)	A2 (Inpatient)	– (1) Sign and symptom present – (3) Site of infection identified – (6)Presence of infection inferred from symptoms only – (10) Prescribed doses of antibiotics correct – (11) Antibiotic in multiple therapy compatible	– (2) Sign and symptom absolute – (4) Potential source of infection present – (5) Presence of infection established by objective data – (7) Antibiotic prescribed alone – (8) Initial antibiotic therapy modified by addition of other antibiotics – (9) Initial antibiotic therapy modified by addition of other antibiotics – (12)Spectra of 2 or more antibiotic in multiple therapy similar – (14)Bacterial morphological and Grams-stain done before therapy initiation – (15) Culture sensitivity test ordered before antibiotic therapy initiation – (16)Culture sensitivity test performed in the course of antibiotic therapy – (17)Antibiotic based on culture sensitivity test results	Gastroenteritis	Penicillin G Gentamicin Metronidazole
87 (Maluti - 368)	B (Outpatient)	– (1) Sign and symptom present – (3) Site of infection identified – (6)Presence of infection inferred from symptoms only – (9) Antibiotics in multiple therapy compatible	– (2) Sign and symptom absolute for bacterial infection – (4) Potential source of infection present – (5) Presence of infection established by objective data – (6) Presence of infection inferred from symptoms only – (7) Antibiotic prescribed alone	Cough (no description) Chest pain	Co-trimoxazole Nitrofurantoin

Prescription Record number	Prescription category	Notation on prescription conformity to applicable criteria		Diagnosis/ Symptom(s)	Prescribed antibiotic(s)
		YES: Prescription conformed to indicated criteria (Criteria number in parenthesis)	NO: Prescription did not conform to indicated criteria (Criteria number in parenthesis)		
			– (8) Dose correct – (10) Spectra of activity of 2 or more prescribed antibiotics similar – (11) Prescribed antibiotic (s) indicated against possible pathogens		
20 (Queen II -19)	B (Inpatient)	– (1) Sign and symptom present – (2) Sign and symptom absolute for bacterial infection – (3) Site of infection identified – (6) Presence of infection inferred form symptoms only – (9) initial antibiotic modified by substitution of other antibiotics – (10) Prescribed doses of antibiotics correct – (11) Antibiotic in multiple therapy compatible – (12)Spectra of activity of 2 or more antibiotics in multiple therapy similar – (13) Prescribed antibiotic(s) indicated against most possible pathogens associated with infection	– (4) Potential source of infection present – (5) Presence of infection established by objective data – (7) Antibiotic prescribed alone – (8) Initial antibiotic treatment modified by addition of other antibiotics – (14)Bacterial morphological and Grams-stain done before therapy initiation – (15) Culture sensitivity test ordered before antibiotic therapy initiation – (16)Culture sensitivity test performed in the course of antibiotic therapy – (17)Antibiotic based on culture sensitivity test results	Gangrene Septicaemia	Cefotaxime Metronidazole Penicillin G Gentamicin
	C (outpatient)	Nil	Nil	Nil	Nil
10 (Queen II -9)	C (Inpatient)	– (1) Sign and symptom present – (2) Sign and symptom absolute for bacterial infection – (3) Site of infection identified – (5) Presence of infection established by objective data – (10) Prescribed doses of antibiotics correct – (11) Antibiotic in multiple therapy compatible – (13) Prescribed antibiotic(s) indicated against most possible	– (4) Potential source of infection present – (6) Presence of infection inferred from symptoms only – (7) Antibiotic prescribed alone – (8) Initial antibiotic treatment modified by addition of other antibiotics – (9) initial antibiotic modified by substitution of other antibiotics – (12) Spectra of activity of 2 or more antibiotics in multiple therapy similar – (14) Bacterial morphological and Grams-stain done before therapy	Septic ulcers/bedsores	Cloxacillin, Gentamicin, Metronidazole

Prescription Record number	Prescription category	Notation on prescription conformity to applicable criteria		Diagnosis/ Symptom(s)	Prescribed antibiotic(s)
		YES: Prescription conformed to indicated criteria (Criteria number in parenthesis)	NO: Prescription did not conform to indicated criteria (Criteria number in parenthesis)		
		pathogens associated with infection – (16)Culture sensitivity test performed in the course of antibiotic therapy o (17)Antibiotic based on culture sensitivity test results	initiation – (15) Culture sensitivity test ordered before antibiotic therapy initiation		
465 (Queen II -569	D (Outpatient)	– (3) Site of possible infection identified – (4) Potential source of infection present – (6)Presence of infection inferred from symptoms only – (7) Antibiotic prescribed alone – (8) Dose correct – (9) Antibiotics in multiple therapy compatible	– (1) Sign and symptom present o (2) Sign and symptom absolute for bacterial infection o (5) Presence of infection established by objective data		
11 (Queen -10	D (Inpatient)	– (3) Site of possible infection identified – 4) Potential source of infection present – (10) Prescribed doses of antibiotics correct – (11) Antibiotic in multiple therapy compatible – (13) Prescribed antibiotic(s) indicated against possible pathogens associated with site of infection	– (1) Sign and symptom present – (2) Sign and symptom absolute for bacterial infection – (7) Antibiotic prescribed alone – (8) Initial antibiotic treatment modified by addition of other antibiotics – (9) initial antibiotic modified by substitution of other antibiotics – (12) Spectra of activity of 2 or more antibiotics in multiple therapy similar	Laparatomy (Surgical wound prophylaxis)	Ampicillin. Metronidazole Gentamicin
742 (Maluti-360)	E (Outpatient)	– (3) Site of possible infection identified – (4) Potential source of infection present – (7) Antibiotic prescribed alone o (8) Dose correct	o (1) Sign and symptom present o (11) Prescribed antibiotic (s) indicated against most possible pathogens associated with site of infection	Non-septic surgical wound	Amoxycillin

Prescription Record number	Prescription category	Notation on prescription conformity to applicable criteria		Diagnosis/ Symptom(s)	Prescribed antibiotic(s)
		YES: Prescription conformed to indicated criteria (Criteria number in parenthesis)	NO: Prescription did not conform to indicated criteria (Criteria number in parenthesis)		
184 Motebang-191	E (Inpatient)	– (3) Site of possible infection identified – 4) Potential source of infection present – (10) Prescribed doses of antibiotics correct o (11) Antibiotic in multiple therapy compatible o (12) Spectra of activity of 2 or more antibiotics in multiple therapy similar o (13) Prescribed antibiotic(s) indicated against possible pathogens associated with site of infection	– (1) Sign and symptom present – (7) Antibiotic prescribed alone – (8) Initial antibiotic treatment modified by addition of other antibiotics – (9) initial antibiotic modified by – substitution of other antibiotics	Urinary retention	Ciprofloxacin Nitrofurantoin
767 (Maluti-39)	F (Outpatient)	– (6) Presence of infection inferred from symptoms – (7) Antibiotic prescribed alone o (8) Dose correct o (11) Prescribed antibiotic (s) indicated against most possible pathogens associated with site of infection	o (1) Sign and symptom present – (4) Potential source of infection present – (5) Presence of infection not established by objective data	Cough (dry)	Erythromycin
198 (Berea - 205)	F (Inpatient)	– (7) Antibiotic prescribed alone – (10) Prescribed doses of antibiotics correct	– (1) Sign and symptom present – (2) Sign and symptom absolute for bacterial infection o 4) Potential source of infection present	Asthma	Ampicillin

Appendix 6

Guidelines for interpreting case note indicated diagnosis/symptom complexes in the establishment of the presence or absence of bacterial infections.

Case note indicated diagnosis/symptom complexes	Literature information on etiological factors causing diagnosis/ symptom complex	Comments for making decision on the presence or absence of infection	Symptom or Diagnosis possibly an indication of infection? If "yes" Is it absolute or not absolute for bacterial infection?	
			Possible	Absolute
1. CASE NOTE INDICATED DIAGNOSES AND SYMPTOM COMPLEXES RELATING TO DISEASES/ INFECTIONS OF THE RESPIRATORY TRACT				
i. Asthma	Chronic inflammatory airway disease characterised by increased responsive ness of the tracheobronchial to a multiplicity of stimuli. Etiology: Atopy is the single largest risk factor. Stimuli inciting acute episode allergens, pharmacologic agents, environmental and occupational substances, as well as infections and exercise. Respiratory viruses and not bacteria or allergy to micro-organisms are the major etiologic factors. **(Mcfadden, 2005:1508,1510)**	Diagnosis of asthma is strictly considered as not to be having bacterial etiology. Presence of infection may be in light of what other symptoms may be indicated in case notes.	No	Not applicable (N/A)
ii. Acute Bronchitis	An inflammation of the bronchi with short a short course < 3 weeks. Etiological factors: exposure to cold, irritant substances and acute infection either viral or bacterial. Fever, coughing with chest pain and dyspnoea may demonstrate as symptoms. **(Weinberger, 2005:205)**	Diagnosis of bronchitis on clinic visits are assumed to be acute if not indicated so in case notes.	Yes	No
iii. Chest pain	Chest pain as a symptom may demonstrate in conditions affecting organs through out the thorax and abdomen **(Lee, 2005:76)** e.g. myocardial ischaemia, diseases of the aorta e.g. aortic dissection, pulmonary embolism, pneumothorax, pneumonia, neuromuscular conditions affecting the intercostal muscles and also gastrointestinal conditions e.g. oesophageal pain **(Lee, 2005:78)**. Chest soreness which may present as pain in the chest is also a complication of coughing **(Weinberger, 2005:206)** which in itself is caused by other etiological factors including viral and bacterial infections of the respiratory system.	Chest pain is interpreted as indicating presence or absence of bacterial infection depending on what other signs or symptoms of infection are noted in case notes or the diagnosis for which the chest pain has been reported as a symptom.		
		Chest pain indicated as the only symptom - interpreted as sign of infection not absolute for bacterial infection.	Yes	No
		Chest pain with objective data establishing lesions	Yes	Yes
iv. Chronic Bronchitis	An obstructive airways disease characterised with chronic cough and phlegm production. Principal etiological factors: cigarette smoke, air pollution and occupational exposure to dust. Respiratory infections, both viral and bacterial may be implicated in the	Chronic bronchitis with coughing and expectoration of coloured white or colourless slimy phlegm considered not to have bacterial infection as etiology	No	N/A

Case note indicated diagnosis/symptom complexes	Literature information on etiological factors causing diagnosis/ symptom complex	Comments for making decision on the presence or absence of infection	Symptom or Diagnosis possibly an indication of infection? If "yes" is it absolute or not absolute for bacterial infection?	
			Possible	Absolute
	development, exacerbation and progression of condition (**Reilly *et al*.2005: 1547**). Implicating pathogens : *S. pneumoniae, H. influenzae, Moraxella catarhalis* as well as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* (**Reilly *et al*.2005: 1553**)			
		Chronic bronchitis with coughing and expectoration of coloured sputum is taken to have bacterial infection as	Yes	Yes
v. Coughs	Explosive expiration that provides a normal mechanism for clearing the tracheobronchial tree of secretions and foreign material. Triggered by a variety of irritant stimuli from both exogenous (smoke, dust fumes , foreign bodies) or endogenous (upper airway secretions , gastric contents) origins or by airway inflammation (viral or bacterial etiology), constriction(as in asthma), infiltration (neoplasms) or compression(extrinsic masses including lymph nodes, mediastinal tumours and aortic aneurysms). Other etiologies of cough include parenchymal lung disease including pneumonia and lung abscess, congestive cardiac failure (CCF), drugs e.g. angiotensin converting enzyme (ACE) inhibitors **(Weinberger, 2005:205)**. Acute cough (< 3 weeks) most often due to respiratory infections or more serious disorders e.g. pneumonia, pulmonary embolus, and CCF. Chronic cough (> 3 weeks) in smoker may be due to Chronic obstructive airways disease or bronchogenic carcinoma which in a non-smoker who is not on ACE inhibitors it may be due to postnasal drip, asthma and gastroesophageal reflux. Purulent sputum suggests bronchitis, bronchiectasis, pneumonia or lung abscess and are indicative of bacterial etiology **(Weinberger, 2005:206)**. Expectoration of blood (Haemoptysis) may be seen in acute or chronic bronchitis due to inflammation of tracheobronchial tree or by neoplasms which studies have shown are the most common causes. Haemoptysis is also seen in tuberculosis and bronchiectasis. Large number of patients	Decision on presence of bacterial pathogen as etiology for cough made on the basis of the nature of cough as described or the presence of other signs and symptoms as stated in case notes.		
		Cough without any description	No	N/A
		Dry or non productive cough if due to respiratory infection will be more of viral than bacterial origin.	No	N/A
		Cough with colourless phlegm	No	N/A
		Cough with coloured sputum	Yes	Yes
		Cough with blood stained sputum	Yes	No
		Cough with respiratory distress	Yes	Yes
		Chronic cough in smoker	Yes	No
		Chronic cough in non smoker	Yes	No

Case note indicated diagnosis/symptom complexes	Literature information on etiological factors causing diagnosis/ symptom complex	Comments for making decision on the presence or absence of infection	Symptom or Diagnosis possibly an indication of infection? If "yes" is it absolute or not absolute for bacterial infection?	
			Possible	Absolute
	may not have identifiable etiology for their hemopstatis **(Weinberger, 2005:207).**			
vii. Emphysema	Type of chronic obstructive airways disease (COAD) characterised by destruction and enlargement of the lung alveoli. Principal etiological factors: cigarette smoke, air pollution and occupational exposure to dust. Respiratory infection may be implicated in the development, exacerbation and progression of condition COAD. Implicating pathogens : *S. pneumoniae, H. influenzae, Moraxella catarrhalis* as well as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* **(Reilly *et al.*2005: 1547-1553)**	Diagnosis of emphysema	Yes	No
Respiratory tract infection (RTI)		Diagnosis of RTI without mention of type or symptoms is vague with respect to identification of etiological factors of such an infection. Such indicated diagnosis in case notes would be taken as being of either viral or bacterial origin	Yes	No
Lower respiratory tract infection (LRTI)		Diagnosis of LRTI	Yes	Yes
Pneumonia	An infection of the alveoli, distal airways and interstitium of the lung clinically manifesting as a constellation of symptoms and signs that may include fever, chills, cough, pleuritic chest pain, sputum production, increased respiratory rate, dullness on percussion, bronchial breathing, crackles and opacity on chest x-ray. **(Marie *et al.*2005:1528)** Most cases of pneumonia acquired in the community are caused by few common respiratory bacterial pathogens including *S. pneumoniae, H. influenzae, S. aureus, Mycoplasma pneumoniae, Moraxella catarrhalis, Legionella* spp, aerobic gram-negative bacteria and viruses e.g. influenza viruses, adenoviruses and	Diagnosis of pneumonia in out patients (may be caused by both bacterial pathogens and viruses)	Yes	No
		Diagnosis of pneumonia in patients on admission has bacteria pathogens as a more probable etiology and is hence considered as absolute for bacterial infection.	Yes	Yes
		TB has a definite causative organism a defined	Yes	No

Case note indicated diagnosis/symptom complexes	Literature information on etiological factors causing diagnosis/ symptom complex	Comments for making decision on the presence or absence of infection	Symptom or Diagnosis possibly an indication of infection? If "yes" is it absolute or not absolute for bacterial infection?	
			Possible	Absolute
	respiratory syncytial viruses(**Marie *et al*.2005:1530**).Hospital acquired pneumonia are caused mainly by gram-negative bacteria including *P. aeruginosa, Acinebacter, Klebsiella pneumoniae* and enteric pathogens e.g. *Enterobacter* spp as well as *S. aureus* and *S. pneumoniae* **(Marie *et al*. 2005:1539)**	treatment protocol which is not part of study. Diagnosis of Pneumonia complicated with TB not considered absolute for other bacterial infections.		
Pneumothorax	Defined as presence of gas in the pleural space. Said to be spontaneous when it occurs without antecedent trauma to the thorax. Basically 2 types of spontaneous pneumothorax, namely primary and secondary spontaneous pneumothoraces. Primary and secondary spontaneous pneumothoraces respectively occur in the absence and presence of underlying lung diseases. Traumatic pneumothoraces result from both penetrating and non penetrating chest trauma. **(Light, 2005:1568)**	Pneumothorax could be a complication of a lung disease and not a sign or symptom of infection per se		
		Diagnosis of pneumothorax in absence of lung disease	No	N/A
		Pneumothorax in presence of lung disease	Yes	Yes
Pleural effusion	Excess quantity of fluid in the pleural space and occurs when fluid formation in the space exceeds fluid absorption. . **(Light, 2005:1565)** It may occur in conditions of congestive cardiac failure, Hepatic cirrhosis (hepatic hydrothorax), Para pneumonic effusion as seen in bacterial pneumonia and lung abscess or bronchiectasis, (**Light, 2005:1566**) Tuberculosis pleuritis, pulmonary embolism. **(Light, 2005:1567)**	Pleural effusion has variety of etiologies including bacterial and viral infections	Yes	No
Haemothorax	Bloody pleural effusion (**Light, 2005:1567)**	As for pleural effusion	Yes	No
Pneumocystis carinii pneumoniae	Pneumocystis carinii pneumonia (PCP) is pneumonia caused by Pneumocystis *carinii* is an opportunistic fungal pulmonary pathogen. Patients with pneumocytosis develop dyspnoea, fever and non-productive cough. **(Walzer, 2005:1194)**	Though bacteria is not its etiologic agent, the treatment of PCP is effected by the use of antibacterial drugs that inhibit folic acid synthesis e.g. Trimethoprim-sulfamethoxazole (Walzer, 2005:1195) and a diagnosis of PCP will justify the prescription of the relevant antibacterial agents for	Yes	Yes

Case note indicated diagnosis/symptom complexes	Literature information on etiological factors causing diagnosis/ symptom complex	Comments for making decision on the presence or absence of infection	Symptom or Diagnosis possibly an indication of infection? If "yes" is it absolute or not absolute for bacterial infection?	
			Possible	Absolute
		the patient		
Upper respiratory tract infection (URTI)	URTI typically refers to infections of the sinus, ear, pharynx, larynx, epiglottis and tonsils or non specific infections of the upper airways variously described as acute infective rhinitis, acute rhinopharyngitis, nasopharyngitis, acute coryza, catarrh or common cold. Most URTIs are caused by viruses and only few are caused by bacteria. Signs and symptoms of bacterial and viral URTIs are however indistinguishable making judicious use of antibiotics in the setting challenging. **(Rubin et al, 2005:185)**	A diagnosis of URTI without indication any inflammation of specific structures in the upper airways will be taken as a sign of infection which is not definite for bacteria	Yes	No
i. Non-specific URTI	Nearly all non specific URTIs are caused by viruses **(Rubin *et al*, 2005:185)**	Diagnosis of common cold, rhinitis coryza and other forms of non specific URTIs will be taken as having viral etiology.	No	N/A
ii. Sinusitis	Inflammatory condition of structures surrounding the nasal cavity caused by infections by a variety of pathogens including viruses, bacteria and fungi resulting from retained secretions in the sinus. **(Rubin *et al*, 2005:185)**May be acute or chronic with most cases of the acute form being diagnosed in the ambulatory care setting and occur primarily as a consequence of a preceding viral infection. Most commonly implicating organisms: *S. pneumoniae, H influenzae and M. catarrhalis. S. aureus* (community acquired); *S. aureus, P. aeruginosa, Klebsiella pneumoniae, Enterobacter spp, Serratia marcescens* (nosocomial). Fungi are also established causes but most acute cases are seen in immunocompromised patients. **(Rubin *et al*, 2005:186).**	Differentiating acute bacterial infections from viral infections on clinical grounds is difficult resulting in antibiotics being prescribed in 85 -98% of all cases. (Rubin *et al*, 2005:186)	Yes	No
iii. Otitis Externa/Media /Ear ache	Otitis externa: Bacterial infections of the auditory meatus resulting from heat, retained moisture and desquamation and maceration of the outer canal epithelium. It may be localised, diffuse, chronic or invasive Implicating pathogens: *P. aeruginosa* and other gram –ve bacteria, S. *aureus, S epidermidis Aspergillus and Actinomyces*) **(Rubin et al, 2005:188**). Otitis media: Bacteria pathogen mediated inflammation of middle ear structures. Implicating pathogens: *S.*	Diagnosis of ear earaches is taken to have the same etiology as otitis media and otitis externa.	Yes	Yes

Case note indicated diagnosis/symptom complexes	Literature information on etiological factors causing diagnosis/ symptom complex	Comments for making decision on the presence or absence of infection	Symptom or Diagnosis possibly an indication of infection? If "yes" is it absolute or not absolute for bacterial infection?	
			Possible	Absolute
	pneumoniae (most commonly implicated pathogen) *M. catarrhalis*, and *H. influenzae*. **(Rubin *et al*, 2005:189)**			
iv. Pharyngitis	Most common presenting symptom is sore throat. Respiratory viruses (rhino viruses, corona viruses, influenza and parainfluenza viruses and adenoviruses) are the most common causes. Acute bacterial pharyngitis is typically caused by S. pyogenes and other *Streptococci* spp as well as *N. gonorrhoeae, Corynebacterium diphtheriae, Yersenia enterocolitica* and *Treponema pallidum* in a minority of cases. **(Rubin *et al*, 2005:190)**	Pharyngitis has both viral and bacterial etiologies which are difficult to differentiate on clinical grounds	Yes	No
v. Laryngitis	Inflammatory process involving larynx caused by a variety of infectious and non infectious processes. Characterised by hoarseness, reduced vocal pitch and aphonia. Acute laryngitis is predominantly caused by the same viruses responsible for other infections of the upper respiratory tract (URT). It can also be associated with acute bacterial respiratory infections such as Group A *Streptococcus* or *C. diphtheriae, M. catarrhalis* **(Rubin *et al*, 2005:192)**	Like other infections of the URT laryngitis could be of viral and bacterial origin	Yes	No
vi. Epiglottitis	Rapidly progressive cellulitis of the epiglottis and surrounding structures that can result incomplete and potential fatal air way obstruction. Established etiology is bacterial infection with Group A Streptococcus, S. pneumoniae, H. parainfluenzae and S. aureus being the most implicated bacteria. Viruses have not been established as a cause of epiglottitis **(Rubin *et al*, 2005:192).**	Epiglottitis has mainly bacterial etiology.	Yes	Yes
vii. Tonsilitis	Inflammation of the tonsils and surrounding structures. May present as sore throat with or without tonsillar exudates or peritonsilar abscesses. May be caused by infections of the URT, both bacterial or viral)	Diagnosis without any description of appearance of tonsils or a description that does not indicate presence of exudates on tonsils would be taken as being of bacterial or viral etiology	Yes	No
		Description of exudates on tonsils indicates bacterial etiology	Yes	Yes
viii. Silicosis	Pulmonary fibrosis resulting from exposure to free silica or crystalline	Diagnosis of silicosis in absence of other	No	N/A

Case note indicated diagnosis/symptom complexes	Literature information on etiological factors causing diagnosis/ symptom complex	Comments for making decision on the presence or absence of infection	Symptom or Diagnosis possibly an indication of infection? If "yes" is it absolute or not absolute for bacterial infection?	
			Possible	Absolute
	quartz as can be found in such occupational environments as mining, stone cutting, and abrasive industries. Patients with silicosis are at greater risk of acquiring infections of *Mycobacterium tuberculosis* and atypical mycobacteria. **(Speizer, 2005:1521)**	symptoms indicating presence of other infection does not have bacterial etiology justifying the prescription of antibiotics other than antituberculosis drugs.		
2. CASE NOTE INDICATED DIAGNOSES AND SYMPTOM COMPLEXES RELATING TO **DISEASES/ INFECTIONS** OF THE **GASTRO INTESTINAL TRACT**				
Abdominal pain	Pain originating in the abdomen may be due to many etiologies including parietal or peritoneal inflammation which may be bacterial contamination or chemical irritation, mechanical obstruction of hollow viscera, vascular disturbances e.g. embolism, vascular rupture or sickle cell anaemia, abdominal wall distortion or traction of mesentery, trauma or infection of abdominal muscles, distension of visceral surfaces. Abdominal pain can also be due to referred pain form extra-abdominal sources e.g. thorax, spine or genitalia, from metabolic(e.g. uraemia, diabetic ketoacidosis, porphyria) and neurogenic causes **(Silen, 2005:82)**	Abdominal pain has varied etiology and needs to be properly diagnosed before therapy of any kind is initiated. Etiological factors may be considered to be of bacterial and non bacterial origin for the purpose of this study	Yes	No
Appendicitis	Luminal obstruction, mucosal inflammation and ulceration of the appendix. Characterised by a steady and severe somatic pain with tenderness. Usually located in the right lower quadrant. The pain is aggravated by motion or cough. Anorexia is common while nausea and vomiting may occur in about 50 – 60 % of case. Luminal bacteria are involved in the pathogenesis of the disease. (Sirren,2005:1806) Infection with Yersinia organisms is particularly suspected. **(Sirren,2005:1805)**	Appendicitis has bacterial etiology.	Yes	Yes

Case note indicated diagnosis/symptom complexes	Literature information on etiological factors causing diagnosis/ symptom complex	Comments for making decision on the presence or absence of infection	Symptom or Diagnosis possibly an indication of infection? If "yes" is it absolute or not absolute for bacterial infection?	
			Possible	Absolute
Dental and mouth infections	Buccal cavity, and structures therein – tooth, periodontium, gingiva etc- are often sites of bacterial infections in absence of good mouth and dental hygiene. *Streptococcus mutans* and other bacteria are often implicated in the formation plaques which if not removed demineralise the tooth enamel and begin processes of tooth decay, inflammation of tooth pulp, gingiva, the periodontium and other structures with the formation of dental abscesses. **(Durso, 2007: 194)** Most oral mucosal diseases involve microorganisms and include viral infections e.g. primary acute herpetic gingivostomatitis, infectious mononucleosis, herpangina, chicken pox, recurrent intraoral herpes simplex etc; bacterial infections e.g. acute necrotising ulcerative gingivitis characterised with painful bleeding gingival, primary, secondary and tertiary syphilis infections of the oral mucosa palate and tongue, gonorrhoea etc; fungal infections e.g. candidiasis. Non infectious etiologies of ulcerative lesions also exist and include for example dermatologic diseases such as mucous membrane pemphigoid that typically produces marked gingival erythema and ulceration, Stevens-Johnson syndrome (erythema multiforme) affecting primarily the skin and hands and other conditions e.g. squamous cell, acute myeloid leukaemia carcinoma and lymphoma all of which may show symptoms of mouth ulcerations and gingival swelling. Parotiditis (Parotitis)Inflammation of parotid gland caused by viruses e.g. mumps virus, and coxsackievirus and by bacteria including *S. aureus, Pneumococcus & Streptococcus* Tooth ache may originate from both dental (caries and abscesses) non-dental (e.g. myofacial pain referred from masticatory muscles or temporomandibular disorder which demonstrates in some patients with rheumatoid arthritis**(Durso, 2007: 195-199)**	Decision on presence of bacterial pathogen as etiology for dental and mouth infections was made on the basis of the nature of diagnosed condition and presence of other signs and symptoms as stated in case notes as shown below.		
		Dental abscess	Yes	Yes
		Periodontitis	Yes	Yes
		Gingivitis	Yes	No
		Gingivitis with bleeding	Yes	Yes
		Mouth ulcers	Yes	No
		Parotiditis	Yes	No
		Oral candidiasis	No	N/A
		Tooth ache	Yes	No

Case note indicated diagnosis/symptom complexes	Literature information on etiological factors causing diagnosis/ symptom complex	Comments for making decision on the presence or absence of infection	Symptom or Diagnosis possibly an indication of infection? If "yes" is it absolute or not absolute for bacterial infection?	
			Possible	Absolute
Gastritis	Gastritis strictly refers to histologically documented inflammation of gastric mucosa. It is not interchangeable with dyspepsia. Two types - Acute and Chronic. Acute gastritis (AG): Presents with sudden onset of epigastric pain, nausea and vomiting. Histological studies of the mucosa shows marked infiltrate of neutrophils with oedema and hyperaemia. Acute infection with *Helicobacter pylori* is mostly responsible. Bacterial infection of the gastrium other than *H. pylori* is rare but potentially life threatening. Implicating organisms include streptococci, staphylococci, *E. coli, Proteus* and *Haemophilus* spp. AG may also have mycobacterial, syphilitic viral, parasitic and fungal etiologies. Chronic gastritis (CG) initially involves inflammation of superficial and glandular portions of the gastrium which then progresses to more severe glandular destruction, with atrophy and metaplasia. It may have an autoimmune etiology where the fundus and body are mainly involved or an *H. pylori* related cause with antral dominance. Stress related mucosal injury demonstrating as acute erosive gastric mucosal changes or frank ulceration with bleeding is classified as stress induced gastritis or ulcers. It results from shock, sepsis, massive burns, severe trauma or head injury and is observed in the acid producing portions of the stomach **(Valle, 2005: 1760-1761)**	Except supported by histological findings a diagnosis of gastritis would be interpreted in light of other presenting symptoms and decisions on the presence or absence of infecting bacterial pathogens as etiological factors made accordingly.		
		Diagnosis of **gastritis** without any defining symptoms	Yes	No
		Diagnosis of **gastritis** with epigastric pain, vomiting and nausea	Yes	No
		Diagnosis of gastritis with gastric bleeding	No	N/A
Gastroenteritis/ Diarrhoea	Gastroenteritis causes profuse watery diarrhoea often with nausea, vomiting**(Silen, 2005:1807.)** and fever, particularly if of infectious etiology. Diarrhoea as a diagnosed condition may be acute (< 2 weeks duration) persistent (2-4 weeks) and chronic (>4 weeks), More than 90% of cases are caused by infectious agents such as bacteria (*E. coli, Klebsiela pneumoniae, Clostridium perfringens, S. aureus,, Salmonella, Shigella*) **(Ahlquist and Camilleri, 2005:**	Gastroenteritis and / or acute diarrhoea have varied etiology.	Yes	No

Case note indicated diagnosis/symptom complexes	Literature information on etiological factors causing diagnosis/ symptom complex	Comments for making decision on the presence or absence of infection	Symptom or Diagnosis possibly an indication of infection? If "yes" is it absolute or not absolute for bacterial infection?	
			Possible	Absolute
	225); enteric viruses e.g. rotaviruses, noroviruses, sapoviruses, astrovruses and adenoviruses with noroviruses causing the condition in all ages while the others are associated with childhood gastroenteritis only. (**Parashar and Glass, 2005:1140**); protozoa (*Entamoeba histolica*, *Giardia* organisms, cryptosporidiosis) and helminths. Non gastrointestinal infectious etiologies include several systemic infections e.g. *viral hepatitis, listeriosis, legionellosis* and *toxic shock syndrome*. Invasive bacteria and *E. histolica* often cause bloody diarrhoea (**Ahlquist and Camilleri, 2005:226)** Other causes of acute diarrhoea include side-effects from medications, ischaemic colitis and colonic diverticulitis. **(Ahlquist and Camilleri, 2005: 226)** Chronic diarrhoea lasting for >4 weeks are non infectious **(Ahlquist and Camilleri, 2005: 227)**	Gastroenteritis with mucoid or bloody diarrhoea caused by invasive bacteria	Yes	Yes
		Chronic diarrhoea	No	N/A
Gastrointestinal infections		Case indicated diagnosis of gastrointestinal infections was interpreted as diagnosis of Gastroenteritis or diarrhoea as above.		
Anal fistulas	Anal fistulas (Fistula ano) is defined as a communication of an abscess cavity with an identifiable internal opening within anal canal **(Gearhart and Bulkley, 2005:1802)**	Presence of abscess is an indication of infection	Yes	Yes
Anorectal abscess, anal sores, perianal ulcers	Anorectal abscess results from an infection involving the glands surrounding the anal canal. Entry of stool into these glands results in infection. **(Gearhart and Bulkley, 2005:1802)**	Abscess are clear cases of infection	Yes	Yes
Peptic ulcer disease(PUD)	Defined as disruptions of the mucosal integrity of the stomach and duodenum leading to a local excavation due to active inflammation. Symptom complexes associated with it include burning epigastric pain that is exacerbated by fasting and improved with meals. **(Valle, 2005: 1746)** The condition develops as a result of an imbalance between mucosal protection/repair and aggressive factors responsible for the injury. Gastric acid plays a major role in its	Current concepts has established gastric infection with *H. pylori* as accounting for the majority of PUD and in the treatment of the condition use of antibiotics directed at this single pathogen is advocated. Multiple antibiotic therapy involving the combination use of tetracycline, metronidazole, clarithromycin and amoxicillin and NOT single	Yes	No

Case note indicated diagnosis/symptom complexes	Literature information on etiological factors causing diagnosis/ symptom complex	Comments for making decision on the presence or absence of infection	Symptom or Diagnosis possibly an indication of infection? If "yes" is it absolute or not absolute for bacterial infection?	
			Possible	Absolute
	pathogenesis while *Helicobacter pylori* infection and NSAIDs ingestion are documented as two predominant etiologies causing it. **(Valle, 2005: 1751).**	antibiotic therapies are used for *H. pylori* eradication **(Valle, 2005: 1754).**		
3. CASE NOTE INDICATED DIAGNOSES AND SYMPTOM COMPLEXES RELATING TO **DISEASES/ INFECTIONS** OF THE **GENITOURINARY TRACT**				
Orchitis	Inflammation of the testes. May be due to syphilis, gonorrhoea, filarial and tuberculosis or mumps virus **(Gershon, 2005:1154).**	Orchitis has both bacterial and non bacterial origins	Yes	No
Urethritis/vaginal discharges	Urethritis in both men and women symptomatically demonstrates as purulent or mucopurulent urethral discharge or as pyeuria. Causative organisms include *N. gonorrhoea* and *Chlamydia trachomatis*. Other organisms apart from *C. trachomatis* implicated in non gonococcal urethritis in men include *Trichomonas vaginalis, Mycoplasma genitalium* and *Ureaplasma urealyticum*.. **(Holmes, 2005:763).** Vaginal discharges may invariably be described as being abnormal and without specific symptoms of urethral inflammation. Abnormality could be reported with respect to amount (large) or odour. Such discharges suggest bacterial vaginosis or trichomoniasis. Yellow coloured vaginal discharges are due to increased numbers of neutrophils and may be due to cervicitis or trichomoniasis. **(Holmes, 2005:765.)** Vaginal trichomoniasis produces yellow, purulent vaginal discharge with vulvular irritation. Bacterial vaginosis is characterised by vaginal malodour and increased white discharge. Causative pathogens include *Gardnerella vaginalis*, various anaerobic bacteria and mycoplasmas. **(Holmes, 2005:766)** Vulvovaginal pruritus, burning or irritation is caused by vaginal candidiasis. It is without increased vaginal discharge or malodour. White scanty vaginal discharges sometimes taking the form of thrush-like plaques loosely adhering to the vaginal mucosa may be present. *Candida albicans* is the causative organism *S. aureus* is implicated in ulcerative vaginitis **(Holmes, 2005:768)**	Presence or absence of bacterial etiologies indicated in case notes in the various descriptions of STDs are noted as follows:		
		Penile discharge	Yes	Yes
		Vaginal discharges – purulent or not purulent – copious, yellow and with bad odour with or without irritation	Yes	Yes
		Vaginal (genital) itches with burning and no discharge, no odour	No	N/A
		Vaginitis (bacterial vaginosis)	Yes	Yes
		Vaginal lesion or ulcers,	Yes	No
		Vaginal candidiasis	No	N/A
		Herpetic genital ulcers	No	N/A

Case note indicated diagnosis/symptom complexes	Literature information on etiological factors causing diagnosis/ symptom complex	Comments for making decision on the presence or absence of infection	Symptom or Diagnosis possibly an indication of infection? If "yes" is it absolute or not absolute for bacterial infection?	
			Possible	Absolute
Pelvic inflammatory disease (PID	Term refers to infection that ascends from the cervix or vagina to involve the endometrium and / or fallopian tubes. Infection may extend from the reproductive tract to cause other infectious conditions like peritonitis, perihepatitis, or pelvic abscess. N. gonorrhoea and C. trachomatis are the most implicated organisms. Other bacteria implicated are *M. genitalia* (significantly associated with endometriosis) anaerobic and facultative organisms e.g. *peptostreptococci, E coli, Haemophillus influenzae* and group B streptococci **(Holmes, 2005:768)**	PID has predominantly bacterial etiology	Yes	Yes
Urinary tract infections (UTI)	UTI: Bacterial infections of the lower and upper anatomic divisions of the urinary tract. Lower UTI: urethritis and cystitis; Upper UTI: acute pyelonephritis, prostatitis and intrarenal and perinephretic abscesses; UTI is defined when pathogenic microorganisms are detected in the urine, urethra, bladder, kidney or prostate. Acute urethral syndrome is termed when dysuria, urgency and frequency with bacteriuria present as symptoms. Many different microorganisms can infect the UT. Most common agents are gram-negative bacilli and include *Escherichia coli* (cause > 80% of infections), *Proteus, Klebsiella* (more commonly associated with patients with calculi, and *Enterobacter, as well as Serratia* and *Pseudomonas* which assumes importance in recurrent infections. Gram + ve cocci are less commonly implicated in UTI. Few such pathogens involved in the infection include *Staphylococcus saprophyticus, Enterococci* and *Staphylococcus aureus S. aureus* is more commonly associated with infection with renal stones or previous instrumentation. Adenoviruses cause acute haemorrhagic cystitis in children. Candida colonisation of the urine of catheterised or diabetic patients may progress to symptomatic invasive UTI **(Stamm, 2005:1715)** CLINICAL PRESENTATIONS OF UTI: CYSTITIS: dysuria, frequency,	Urinary tract infections have mainly bacterial etiology. Diagnosis of UTI in cases notes in absence of any mention of symptoms were considered as infections absolute for bacteria. Where symptom complexes are indicated, decisions on presence or absence of bacterial etiologies would be made depending on said cited symptom complexes.		
		UTI indicated as diagnosis	Yes	Yes
		Cystitis (adults) and cystitis in children without haematuria	Yes	Yes

Case note indicated diagnosis/symptom complexes	Literature information on etiological factors causing diagnosis/ symptom complex	Comments for making decision on the presence or absence of infection	Symptom or Diagnosis possibly an indication of infection? If "yes" is it absolute or not absolute for bacterial infection?	
			Possible	Absolute
	urgency and suprapubic pain. Urine becomes cloudy and malodorous.			
	ACUTE PYELONEPHRITIS: fever chills, nausea vomiting and diarrhoea with symptoms of cystitis either present or not. Symptoms develop rapidly over a few hours.	Cystitis in children with haematuria	Yes	No
	URETHRITIS: may demonstrate same symptoms as cystitis and is difficult to distinguish urethritis from cystitis on clinical grounds.			
	Gross haematuria, suprapubic pain and abrupt onset of illness <3days most likely to be due to E. coli infection. Where onset of symptom is gradual, and there is no haematuria and no suprapubic pain, sexually transmitted pathogens should be suspected.	Pyelonephritis	Yes	Yes
	ACUTE BACTERIAL PROSTATITIS: Characterised by fever, chills, dysuria and a tense extremely tender prostate. Infection is usually due to E. coli or Klebsiella in non catheterised men Spectrum may include nosocomial gram-negative rods and enterococci.	Prostatitis	Yes	Yes
	Chronic bacterial prostatitis: Characterised with a pattern of relapsing infections, obstructive voiding symptoms, perineal pain and low back pain may develop in some men. Infection may intermittently spread to the bladder to produce frequency, urgency and dysuria.			
4. CASE NOTE INDICATED DIAGNOSES AND SYMPTOM COMPLEXES RELATING TO **DISEASES/ INFECTIONS OF SKIN AND SOFT TISSUE**				
Skin &soft tissue infections.	**Abscesses**: Number of pathogens particularly anaerobic bacteria, staphylococci and streptococci provoke the formation of abscesses. **Gerald, 2005:706**	Abscesses	Yes	Yes
	Inflammation: Microbial tissue invasion invoke host inflammatory responses that result from cytokine production or other specific factors. **Gerald, 2005:705.** In soft tissues these may show as swellings	Swellings with traumatic etiology	No	N/A
		Swellings with no evidence of trauma	Yes	Yes
	Panniculitis: Inflammation of the fat. Several forms including erythema nodosum, (commonly associated with streptococcal fungal, mycobacterial, yersinial infections) **Bolognia and Braverman,2005:308**, also drugs and idiopathic causes **Kaye and**	Panniculitis has several etiologies. May be due to systemic disease, microbial infections not necessarily bacterial, or even factitious. But ulcerated forms may become infected		

Case note indicated diagnosis/symptom complexes	Literature information on etiological factors causing diagnosis/ symptom complex	Comments for making decision on the presence or absence of infection	Symptom or Diagnosis possibly an indication of infection? If "yes" is it absolute or not absolute for bacterial infection?	
			Possible	Absolute
	Kaye, 2005:108) erythema induratum, lupus profundus, nodular vasculitis, lipomembranous lipodermatosclerosis, α_1-antitrypsin deficiency, facticial, fat necrosis secondary to pancreatitis. All lesions except, erythema nodosum, may breakdown and ulcerate.	Panniculitis	Yes	No
		Panniculitis (ulcerated)	Yes	Yes
	Pustules: raised lesions containing purulent exudates (leukocytes) Presence of pustules does not necessarily signify the existence of infection. **Lawley and Yancey, 2005:283**	Pustules Infection not necessarily signified	Yes	No
	Seborrhoea: excessive secretions of the sebum. (Seborrhoic dermatitis) Chronic disorder characterised by greasy scales overlying erythematuos patches. Evident within first few weeks of life. Rare in children beyond infancy but may become evident again in adult life. Frequently seen in patients with Parkinson's disease, Cerebrovascular accident, HIV infections but overwhelming majority of individuals with seborrheic dermatitis have no underlying cause. **Mccall and Lawley, 2005:291**	Seborrhoea/seborrheic dermatitis No infectious etiology	No	N/A
	Animal bites: Cat bites and bites and cause cellulitis associated with *Pasteurella multocida, Staphylococcus intermedius* and *Capnocytophaga canimorsus* as well as anaerobic organisms including *Fusobacterium, Bacteroides*, aerobic and anaerobic streptococci and *Eikenella corrodens*.(dog and human bites) **Stevens, 2005:743**	Animal bites introduce various bacteria into the dermis and associated with cellulitis.	Yes	Yes
	Acne vulgaris: self limiting disorder of teenagers and adolescents. Initiated by increased sebum production coupled with formation of small cysts (comedones) that block hair follicles, causing retention of sebum and keratinous material. Activity of bacteria (*Proprionobacterium acnes*) within comedones releases free fatty acids from sebum, causes inflammation within the cyst and rupture	Acne vulgaris: Pathogenesis involves bacterial etiology.	Yes	Yes

Case note indicated diagnosis/symptom complexes	Literature information on etiological factors causing diagnosis/ symptom complex	Comments for making decision on the presence or absence of infection	Symptom or Diagnosis possibly an indication of infection? If "yes" is it absolute or not absolute for bacterial infection?	
			Possible	Absolute
	of cyst wall. **Mccall and Lawley, 2005:294**			
	Burns cause injury to skin and provide means of microbial entry into host organism and hence infection. **Pier, 2005:700**	Burns (Clean)	No	N/A
		Burns (septic)	Yes	Yes
	Cellulitis: Acute inflammatory condition of the skin characterised with localised pain, erythema, swelling and heat caused by indigenous bacteria colonising the skin e.g. *Staphylococcus aureus* or *Streptococcus pyogenes* and a wide variety of exogenous bacteria **Stevens, 2005:743**	Cellulitis: Definite bacterial etiology	Yes	Yes
	Decubitus Ulcers / bed or pressures sores provide means of microbial entry into host organism and hence infection **(Pier, 2005:700)** mostly by bacteria colonising the skin.	Decubitus Ulcers / bed or pressures sores	Yes	Yes
	Chalazion / Blepharitis: Chalazion painless granulomatuos inflammation of a meibomian gland that produces a pealike nodule within the eye lid. Blepharitis refers to inflammation of the eyelids. Staphylococci highly implicated. **Horton, 2005:165**	Chalazia / Blephariti	Yes	Yes
	Conjunctivitis: has allergic, viral or bacterial etiology. Eye is red, irritating with minimal pain. Viral conjunctivitis exhibits watery discharge, mild foreign body sensation and photophobia. Bacteria conjunctivitis tends to produce more purulent exudate	Conjunctivitis: Viral	No	N/A
		Conjunctivitis: allergic	No	N/A
		Conjunctivitis: Bacterial (Clamydia)	Yes	Yes
	Gangrene: Death of tissue, generally in considerable mass. Associated with loss of vascular supply and followed by bacterial infection and putrefaction. Commonly associated organisms include group A *Streptococcus*, mixed aerobic anaerobic bacteria (necrotising fasciitis) and *Clostridium perfringens* (gas gangrene) **Stevens, 2005:743**	Gangrene	Yes	Yes

Case note indicated diagnosis/symptom complexes	Literature information on etiological factors causing diagnosis/ symptom complex	Comments for making decision on the presence or absence of infection	Symptom or Diagnosis possibly an indication of infection? If "yes" is it absolute or not absolute for bacterial infection?	
			Possible	Absolute
	Genital ulcers: Genital ulceration reflects a set of STI **(Holmes, 2005:771)** Usual causes include herpes simplex, *Treponema pallidum* (primary syphilis, *Haemophillus ducreyi* (chancroid) infections. PCR testing implicates genital herpes as the most common cause of genital ulcers in developing countries. Lymphogranuloma venereum caused by a strain of Clamydia and donovanosis or granuloma inguinale (deep purulent ulceration of the skin of external genitals caused by *Calymmatobacterium granulomatis*). Other causes of genital ulcers include candidiasis and traumatised genital warts, and cutaneuos manifestations of systemic disease e.g. genital ulceration in Steven-Johnson syndrome. **(Holmes, 2005:772)**	Genital ulcers mainly caused by sexually transmitted viral and bacterial diseases.	Yes	No
		Genital swelling. Pathogenesis similar to cellulitis	Yes	Yes
	Impetigo: Common superficial bacterial infection caused by group A β–haemolytic streptococci or *Staphylococcus aureus* Primary lesion is a superficial pustule that ruptures and forms a characteristic yellow brown honey coloured crust. **Mccall and Lawley, 2005:292**	Impetigo	Yes	Yes
	Scabies: Human itch mite (*Sarcoptes scabiei*) infection. Causes itching dermatitis. Female mite borrows superficially beneath the stratum corneum. Itching and rash associated with scabies are derived form sensitization reaction directed against the excreta the mite deposits in the borrows. Scratching kills the mites. This coupled with immunity limits the mites to about <15 per person. Glucocorticoid use and loss of immunity (HIV patients) may cause hyper infection, with mite numbers of > 1000 person (Norwegian or crusted scabies. Bacterial superinfection may occur.	Scabies	Yes	No
	Skin Rashes; temporary eruptions or lesions on the skin. Different types of rashes. ***Macules***- flat lesions defined by an area of changed	Rashes have varied etiologies	Yes	No

Case note indicated diagnosis/symptom complexes	Literature information on etiological factors causing diagnosis/ symptom complex	Comments for making decision on the presence or absence of infection	Symptom or Diagnosis possibly an indication of infection? If "yes" is it absolute or not absolute for bacterial infection?	
			Possible	Absolute
	colour. ***Papules*** –raised solid lesion <5mm in diameter; ***Plaques***: >5mm in diameter with flat plateau like surface; ***Nodules*** > 5mm in diameter with a more rounded configuration. ***Wheals***: pale pink papules or plaques that appear ring like as they enlarge. ***Vesicles*** (<5 mm) and ***bullae*** (>5mm) Circumscribed elevated lesions containing fluid. ***Pustules*** (as above) Vesicular processes may evolve to pustules. ***Nonpappable pupura***: flat lesions due to bleeding into the skin. Termed ***petechiae*** if < 3mm in diameter or ***ecchymoses*** if > 3mm. ***Palpable purpura***: raised lesion that is due to inflammation of the vessel wall (vasculitis) with subsequent haemorrhage. **Kaye and Kaye, 2005:108** Rashes have varied etiology. May be due to viral infections e.g. centrally distributed maculopapular eruptions of measles and other viral infections e.g. Epstein-Barr virus, human parvovirus and human herpes virus, varicella zoster virus causing vesiculobollous eruptions; drug induced (centrally distributed rashes); bacterial e.g. peripheral eruptions of secondary syphilis, confluent desquamative erythemas caused by Streptococcus and Staphylococcus aureus infections and also staphylococcal scalded skin syndrome seen primarily in children and in immunocompromised adults, **Kaye and Kaye, 2005:109**, allergic or connective tissue disease e.g. ulticarial eruptions seen hypersensitivity reactions, systemic lupus erythematuos, malignancy (chronic urticaria with fever), disseminated infection in immunocompromised persons seen as nodular eruption, etc **Kaye and Kaye, 2005:116**			
	Leprosy: Chronic infectious disease caused by Mycobacterium leprae. **Gelber, 2005:966**Clinical features largely confined to skin, peripheral nervous system upper respiratory tract , eyes and testes. Skin manifestations as disease progress from borderline to lepromatuous state are seen as an evolution form asymmetric localised macules and plaques to nodular and indurated symmetric	Leprosy: specific infection associated with M. leprae.	Yes	Yes

Case note indicated diagnosis/symptom complexes	Literature information on etiological factors causing diagnosis/ symptom complex	Comments for making decision on the presence or absence of infection	Symptom or Diagnosis possibly an indication of infection? If "yes" is it absolute or not absolute for bacterial infection?	
			Possible	Absolute
	generalised manifestations. **Gelber, 2005:967**			
Miscellaneous conditions involving skin and soft tissue		Lacerations and bruises (non septic).		
		Lacerations and bruises septic		
		Deep wounds (non septic) gunshot or stab)	No	N/A
		Deep wounds (septic)		
		Deep wound (gunshot or stab) Abdominal	Yes	Yes
		Surgical wounds (non septic)	No	N/A
5. CASE NOTE INDICATED DIAGNOSES AND SYMPTOM COMPLEXES RELATING TO **BONES**				
Fractures		Fractures with no open wound. Considered uninfected	No	N/A
		Fractures with open wound (non septic) Considered uninfected	No	N/A
		Fractures with open wound (non septic)	Yes	Yes
		Fractures with prosthetic substitution (non septic) Considered uninfected	No	N/A
Osteomyelitis	An infection of bone caused mostly by pyrogenic bacteria and mycobacteria. Haematogenous osteomyelitis affects mainly children mainly. Single long bones are affected. Child with osteomyelitis appears acutely ill with high fever, chills and localised pain and restriction of movement & difficulty to bear pain. Vertebral bodies most common sites of acute haematogenous osteomyelitis in adults. Commonly isolated organisms include S. aureus, Group B Streptococci, E. coli. Vertebral osteomylitis is due mainly to E. coli and other enteric bacilli. Osteomyelitis secondary to a focus of infection, including infections introduced by penetrating injuries e.g. bites, puncture wounds and open fractures, accounts for about 80% of all cases of osteomyelitis and is seen mainly in adults. *Staph aureus* isolated in >50% of cases. Infections are more often polymicrobial and are likely to involve gram-negative and anaerobic.	Osteomylitis: Diagnosis of osteomyelitis considered absolute case of bacterial in infection of bone	Yes	Yes

Case note indicated diagnosis/symptom complexes	Literature information on etiological factors causing diagnosis/ symptom complex	Comments for making decision on the presence or absence of infection	Symptom or Diagnosis possibly an indication of infection? If "yes" is it absolute or not absolute for bacterial infection?	
			Possible	Absolute
	Immunocompromised patients may rarely develop osteomyelitis form atypical mycobacteria, Pneumocystis, Candida, Cryptococcus or Aspergillus (**Parsonnet and Maguire, 2005:745 & 746**			
6. CASE NOTE INDICATED DIAGNOSES AND SYMPTOM COMPLEXES RELATING TO **CNS**				
CNS infections	Distinct clinical syndromes that include acute bacterial meningitis, viral meningitis, encephalitis, focal infections such as brain abscess and subdural empyema, and thrombophlebitis. All may present with non specific prodrome of fever and headache. In healthy individual these may be thought of initially to be benign until, with exception of viral meningitis, altered consciousness, focal neurologic signs or seizures appear. Need to distinguish between these conditions and identify offending pathogens **Acute Bacterial meningitis**: Acute purulent infection within subarachnoid space. Associated with a CNS inflammatory reaction that may results in decrease consciousness, seizures raised intracranial pressure and stroke. Meninges, the subarachnoid space and brain parenchyma all frequently involved. *S. pneumoniae* (pneumococcal pneumonia a common predisposing factor) and *N. meningitides* are commonly implicated in adults and children. **Roos L.R., T.L.2005:2471** Enteric gram-negative bacilli are increasingly common cause of meningitis in individual with chronic debilitating diseases such as diabetes, cirrhosis or alcoholism. *L. monocytogenes*: increasing cause of meningitis in neonates >1 year. pregnant women and individuals > 60yrs. *H. Influenzae* cases of meningitis in unvaccinated children and adults. *Staphylococcus aureus and coagulase negative staphylococci* important cause in neurosurgical procedures. Clinical Triad of meningitis: Nuchal rigidity (stiff neck fever and headache. Alterations in mental status occurs in >50% of patients	Meningitis: Diagnosis of meningitis with undefined etiology will be taken as meningitis that could be of bacterial viral or fungal etiology	Yes	No
		Bacterial Meningitis : Definite for bacteria infection	Yes	Yes
		Cryptococcal meningitis definite for fungal infection	No	N/A

Case note indicated diagnosis/symptom complexes	Literature information on etiological factors causing diagnosis/ symptom complex	Comments for making decision on the presence or absence of infection	Symptom or Diagnosis possibly an indication of infection? If "yes" Is it absolute or not absolute for bacterial infection?	
			Possible	Absolute
	and vary from lethargy to coma. **Roos and Tyler, 2005:2472** **Subacute meningitis**: Patient has unrelenting headache, stiff neck, low grade fever and lethargy for days to several weeks before the present for evaluation. Common causative organisms include *Mycoplasma tuberculosis*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Cryptococcus imitis* and *Treptonema pallidum*. **Roos and Tyler, 2005:2472** Most common fungus causing infections is *C. neoformans* found worldwide in bird excreta. T. Pallidum invades CNS early in the course of syphilis.			
	Viral Meningitis: Presents with fever, headache and meningeal irritation coupled with inflammatory CNS profile. Fever may accompanied by malaise, myalgia, anorexia, nausea and vomiting, abdominal pain and /or diarrhoea. Mild degree of lethargy and nausea may be seen .Entero virus account for 75 t0 90% of aseptic meningitis in most cases. Example; coxsackievirus, poliovirus and human enterovirus.. **Roos and Tyler, 2005:2477**	Viral meningitis: definite for viral infection	No	N/A
7. CASE NOTE INDICATED DIAGNOSES AND SYMPTOM COMPLEXES RELATING TO BLOOD				
Septicaemia	Septicaemia is defined as presence of microbes and their toxins in blood and bacteraemia as presence of bacteria in blood. Animals exhibit both systemic responses to microbes that transverse epithelial barriers and invade underlying tissues. Fever or hypothermia, leukocytosis or leukopenia and tachycardia are the cardinal signs of systemic response called systemic inflammatory response syndrome (SIRS) Patient said to have severe systemic syndrome (SIRS) when organs distant from site of infections are involved(SIRS); Septic shock is said to be present when hypotension cannot be corrected by infusing fluids. Severe sepsis can be a response to any class of microorganisms	Diagnosis of septicaemia without symptom complexes or laboratory investigations suggesting bacteraemia	Yes	No
		Diagnosis of septicaemia with symptom complexes or laboratory investigations suggesting	Yes	Yes

Case note indicated diagnosis/symptom complexes	Literature information on etiological factors causing diagnosis/ symptom complex	Comments for making decision on the presence or absence of infection	Symptom or Diagnosis possibly an indication of infection? If "yes" is it absolute or not absolute for bacterial infection?	
			Possible	Absolute
	and microbial invasion is not essential for the development of severe sepsis since local inflammation can also elicit distant organ dysfunction and hypotension.. **Munford,2005:1606** The following conditions may predispose to positive blood cultures with indicated organisms: **Gram –ve bacilli** Diabetes mellitus, Lymphoproliferative diseases Liver cirrhosis, Burns, Invasive procedures/devices, neutropenia, Indwelling Urinary catheters Diverticulitis , perforated viscus **Gram-positive bacteria** Intravascular catheters, Indwelling mechanical devices, Burns, Burns, Intravenous drug use, infection with superantigen –producing streptococcus pyogenes **Fungi** Neutropenia Broad spectrum antimicrobial therapy **Munford,2005:1607**	bacteraemia		
Systemic gonorrhoeal infection	**Gonorrhoea:** commonly sexually transmitted infection of epithelium and commonly manifests as cervicitis, proctitis and conjunctivitis. Un treated infections can lead to endometritis , salpingitis, tuboovarian abscess, bartholinitis, peritonitis and perihepatitis in the female; periurethritis and epididymitis in the male; and ophthalmia neonatorum in the newborn. Gonorrhoea may also disseminate, though rarely, to cause skin lesions, tenosynovitis, arthritis and even meningitis and endocarditis in rare cases. *Neisseria gonorrhoea*, a	Diagnosis of systemic gonorrhoeal infection: symptom complexes confirmed presence of condition	Yes	Yes
		Diagnosis of systemic gonorrhoeal infection: No history of genital gonorrhoea. Not a baby born of gonorrhoeal mother. Symptom complexes not	Yes	No

Case note indicated diagnosis/symptom complexes	Literature information on etiological factors causing diagnosis/ symptom complex	Comments for making decision on the presence or absence of infection	Symptom or Diagnosis possibly an indication of infection? If "yes" is it absolute or not absolute for bacterial infection?	
			Possible	Absolute
	gram-negative nonmotile diplococci is the implicating organism in gonococcal infections. **Ram and Rice, 2005 :855.** Septic arthritis is the most common manifestation of systemic manifestation in the new bom. Onset is s 3- 21 days after birth and polyarticular involvement is common. . Sepsis, meningitis and pneumonia are seen in most cases. Gonococcal arthritis results from gonococcal bacteraemia and occurs in up to 3% of patients untreated gonococcal mucosal infection. Menstruation is a risk factor for dissemination and approximately 66% of cases are in women. Symptoms may appear within 7 days of onset of menses in about 50% of affected women.2 stages of gonococcal septic arthritis: a bacteraemic state with fever accompanied with chills (uncommon) and a joint localised stage with suppurative arthritis. Polyarthralgias usually include knees , elbows and more distal joints. Skin lesions are seen in about 75% of patients. And include papules and pustules. Suppurative arthritis involves one or two joints – knees, writs ankles and elbows. . Presence of genital infection makes it easier to distinguish gonococcal arthritis from septic arthritis caused other pathogens. **Ram and Rice, 2005 :859**	confirming systemic gonorrhoea		
8. CASE NOTE INDICATED DIAGNOSES AND SYMPTOM COMPLEXES RELATING TO **PYREXIAS**				
Enteric (typhoid fever)	Systemic disease characterised by fever and abdominal pain caused by dissemination of *S. typhi or S.paratyphi.* Prodrome of non-specific symptoms often preceded fever and includes chills, headache, anorexia, cough, weakness sore throat, dizziness and muscle pains. Patients may present with diarrhoea or constipation .Diarrhoea more common with AIDS patients and children , 1 yr. of age. Early physical findings : rash hepatosplenomegaly, epistaxis and relative bradycardia. **Lesser and Miller,2005:898**	Diagnosis of Enteric fever	Yes	Yes
Fever & Chills	Elevation of body temperature exceeding normal daily body variation and occurring in conjunction with an increase in hypothalamic set point. Chills result from an increase in hypothalamic set point.	Indication of fever without definite diagnosis	Yes	No

Case note indicated diagnosis/symptom complexes	Literature information on etiological factors causing diagnosis/ symptom complex	Comments for making decision on the presence or absence of infection	Symptom or Diagnosis possibly an indication of infection? If "yes" is it absolute or not absolute for bacterial infection?	
			Possible	Absolute
	Raising hypothalamic set point to higher levels results in activation of neurons in the vasomotor centre and the constriction of peripheral blood vessels. Blood becomes shunted away from the periphery to the internal organs and heat loss from the skin decreases and the person feels cold. Shivering which increases heat production from the muscles may begin at this time. Processes of heat conservation (vasoconstriction) and heat production (shivering and increased metabolic activity continues until temperature of blood bathing the hypothalamic neurons matches the new thermostat setting.. **Dinarelo and Gelfand,2005:105** Etiology: Exogenous pyrogens most of which are microbial products, microbial toxins or whole microorganisms. Classic example of exogenous pyrogen: lipopolysaccharides produced by all gram-negative bacteria. Enterotoxins produced by gram-positive bacteria e.g. *Staphylococcus aureus* and group A&B streptococci. Hyperpyrexia: extraordinarily high temperature developing in patients with severe infections or in patients with central nervous system haemorrhage. **Dinarelo and Gelfand,2005:105**			
		Fever with diagnosis of non bacterial infections (viral infections or neoplasms)	No	N/A
		Fever with definite diagnosis of bacterial infections	Yes	Yes
Fever of unknown origin (FUO)	Defined by Peterdorf and Beeson in 1961 as temperatures of > 38.3°C (>101°F, a duration of fever of >3 weeks and failure to reach diagnosis despite a 3 week patient investigation. New definitions proposed by Durack and Street. (1)Classic FUO similar to definitions of Peterson and Beeson and excludes a one week hospital investigation. (2) Nosocomial FUO – temperature of ≥ 38.3°C (101°F) developing on several occasions in a hospitalised patient who is receiving acute care and in whom infection is not manifest despite at least 2 days of culture incubation. 3. Neutropenic FUO- – temperature of ≥ 38.3°C (101°F) on several occasions in a patient whose neutrophils count is, <500.μL or is expected to fall to that level in 1-2 days and without any specific cause after 3 days of investigation.. HIV associated FUO is defined if	Diagnosis of FUO	Yes	No

Case note indicated diagnosis/symptom complexes	Literature information on etiological factors causing diagnosis/ symptom complex	Comments for making decision on the presence or absence of infection	Symptom or Diagnosis possibly an indication of infection? If "yes" is it absolute or not absolute for bacterial infection?	
			Possible	Absolute
	by a temperature of 38.3.oCon several occasions over a period of 4 weeks for outpatients. 3days of hospitalisation with patients with HIV and investigations reveal no course. Classic FUO: Etiology: Infections, extrapulmonary TB remains the leading cause of FUO. Other causes include prolonged mononucleosis syndromes caused by Epstein Barr virus, cytomegalovirus or HIV. **Gelfand and Callahan, 2005:116**, Others are poorly localized intra-abdominal abscess, renal, retroperitoneal and paraspinal abscesses, renal malacoplakia with submucosal plaques or nodules involving the urinary tract, osteomyelitis with prosthetic implants, fungal disease, particularly histoplasmosis involving reticuloendothelial system. Neoplasms also commonly cause FUO after infections., Multisystem disease is the most common cause of FUO in the elderly. Giant cell arteritis is a leading etiologic entity. Drug fever, pulmonary embolism and factidious fever, are other etiologies. **Gelfand and Callahan, 2005:117**			
Night Sweats	Moderate night sweats common in anxiety states. Drenching sweats more commonly associated with infections or lymphoproliferative diseases. Hope et al,1998:46	Night sweats not necessarily indicative of bacterial infection	Yes	No
9. CASE NOTE INDICATED DIAGNOSES AND SYMPTOM COMPLEXES FOR WHICH BACTERIAL INFECTIONS ARE NOT LITERATURE DOCUMENTED ETIOLOGIES				
Miscellaneous diagnoses / symptom complexes for which antibiotics were prescribed	Atopic Allergy: Familial tendency to manifest such conditions as asthma, rhinitis, urticaria and eczematuous dermatitis alone or in combination.. Associated with IgE. Mast cells are key effector cells of the biologic response in allergic reactions. Fixation of IgE to mast cells and basophils (sensitization) prepares these cells for subsequent antigen-specific activation. **Austen, 2005: 1947.** Etiologies: Predisposing factors to the development of allergy include heterologous proteins in the form of hormones, enzymes, pollen and non pollen extracts, food, antiserum related proteins, venom, polysaccharides, drugs including antibiotics, and other substances that may act as haptens, **Austen, 2005: 1949**	Allergy, Allergic rhinitis, Asthma	No	N/A

Case note indicated diagnosis/symptom complexes	Literature information on etiological factors causing diagnosis/ symptom complex	Comments for making decision on the presence or absence of infection	Symptom or Diagnosis possibly an indication of infection? If "yes" is it absolute or not absolute for bacterial infection?	
			Possible	Absolute
	Anaemia		No	N/A
	Ascites		No	N/A
	Arthritis		No	N/A
	Acute renal failure		No	N/A
	Bronchospasm		No	N/A
	Backache		No	N/A
	Broncho carcinoma		No	N/A
	Bleeding (superficial)		No	N/A
	Blood after urinating		No	N/A
	Bodily pains		No	N/A
	Cough (dry or colourless sputum)		No	N/A
	Common cold/ Influenza		No	N/A
	Dizziness		No	N/A
	Cor-pulmonale		No	N/A
	Congestive cardiac failure		No	N/A
	Cold feet		No	N/A
	Chicken pox		No	N/A
	Cerebrovascular accident		No	N/A
	Dislocation		No	N/A
	Dermatitis		No	N/A
	Diabetes mellitus		No	N/A
	Depression		No	N/A
	Epilepsy/Convulsions		No	N/A
	Eczema		No	N/A
	Epistaxis		No	N/A
	Encephalopathy		No	N/A
	Fracture		No	N/A
	Fungal dermatitis		No	N/A
	Genital itches		No	N/A
	Headache		No	N/A

Case note indicated diagnosis/symptom complexes	Literature information on etiological factors causing diagnosis/ symptom complex	Comments for making decision on the presence or absence of infection	Symptom or Diagnosis possibly an indication of infection? If "yes" is it absolute or not absolute for bacterial infection?	
			Possible	Absolute
	Haemolysis		No	N/A
	Haemorrhoids		No	N/A
	Hypoglycaemia 2º to Diabetes mellitus		No	N/A
	Hyperglycaemia 2º to Diabetes mellitus		No	N/A
	Hyperacidity		No	N/A
	Head injuries		No	N/A
	Hodgkins lymphoma		No	N/A
	Hypertension		No	N/A
	Herpes zoster		No	N/A
	Lymphadenopathy		No	N/A
	Malarial prophylaxis		No	N/A
	Oral thrush		No	N/A
	Pain in the anus		No	N/A
	Paedal oedema of unknown cause		No	N/A
	Pain in the anus		No	N/A
	Pain in the breast		No	N/A
	Pain in the foot /ankle		No	N/A
	Pain in the shoulder		No	N/A
	Paraplegia/Hemiparesis		No	N/A
	Psychosis		No	N/A
	Immunocompromised patient		No	N/A
	Intestinal occlusion		No	N/A
	Kwashiorkor		No	N/A
	Loss of appetite		No	N/A
	Liver cirrhosis		No	N/A
	Loss of weight		No	N/A
	Mumps		No	N/A
	Night sweats		No	N/A
	Retrosternal/Epigastric pain		No	N/A
	Rape		No	N/A

Case note indicated diagnosis/symptom complexes	Literature information on etiological factors causing diagnosis/ symptom complex	Comments for making decision on the presence or absence of infection	Symptom or Diagnosis possibly an indication of infection? If "yes" is it absolute or not absolute for bacterial infection?	
			Possible	Absolute
	Sciatica		No	N/A
	Swollen eyes		No	N/A
	Skin patches		No	N/A
	Skin itches		No	N/A
	Stevens Johnson syndrome		No	N/A
	Tooth ache		No	N/A
	Threatened abortion		No	N/A
	Uteral fibroids		No	N/A
	Vaginal bleeding		No	N/A
	Vaginal candidiasis		No	N/A
	Viral infections		No	N/A
	Vomiting		No	N/A
	Warts		No	N/A
	Yellow urine		No	N/A
	Diagnosis or symptoms not stated		No	N/A

Appendix 7:

Characteristics of antibiotics routinely used in Lesotho (Compiled from : Archer & Polk, 2005: 789 - 806; Chambers 2001:1171-1266)

Antibiotic Name	Structural Classification	Mechanism of action	Spectrum of activity	Infection commonly prescribed for	Compatibility notes
Penicillin G	Penicillin	Inhibition of cell wall synthesis: Bactericidal	Spirochaetes, Aerobic Gram +ve cocci mainly Streptococci spp, few staphylococci, *Neisseria* spp, many fastidious oral bacteria (e.g. *Fusobacterium, Porphyromonas Actinomyces*) *Clostridium* spp (except *C. difficile*)	URTI infections (S. pyogenes), yaws, syphilis, oral periodontal infections, meningococcal meningitis Groups A&B streptococcal infections, viridans endocarditis, clostridial myonecrosis, tetanus, anthrax, rat bite fever.	Incompatible with Tetracyclines, Chloramphenicol, Rifampicin and Ciprofloxacin
Penicillin V	Penicillin	Inhibition of cell wall synthesis: Bactericidal	As above for Penicillin G	As above for Penicillin G	Incompatible with Tetracyclines, Chloramphenicol and Ciprofloxacin
Ampicillin	Penicillin (β-lactam)	Inhibition of cell wall synthesis: Bactericidal	Broad spectrum. As for penicillin in addition to gram-ve bacteria (*E. coli, P mirabilis, Salmonella* spp, Shigella spp, *Haemophillus influenzae.*	Acute otitis media, meningitis caused by H. influenzae & Listeria monocytogenes, meningitis, salmonellosis, E. faecalis associated UTI, NB. High rates of resistance of organisms to antibiotic limits its empirical use. >80% E.coli & P. mirabilis and > 30% H. influenzae resistant.	Incompatible with Tetracyclines, Chloramphenicol Ciprofloxacin, and Rifampicin
Amoxicillin	Penicillin (β-lactam)	Inhibition of cell wall synthesis: Bactericidal	As for ampicillin	As for ampicillin	Incompatible with Tetracyclines, Chloramphenicol, Rifampicin and Ciprofloxacin
Co-Amoxyclav (Augmentin) (Amoxicillin + clavulanic acid) Others: Ampicillin or Ticarcillin, or piperacillin + either clavulanic acid or sulbactam or	Penicillins + β-lactamase inhibitor	Inhibition of cell wall synthesis: Bactericidal	As for Ampicillin but also effective against β-lactamase producing bacteria	Effective in infections due to *E. coli, Klebsiela, Proteus* spp, *H. influenzae, Moraxella catarhalis, Providencia* spp, anaerobes including *Bacteroides*	

tazobactam)					
Cloxacillin [Penicilinase (β-lactamse) resistant Penicillin]	Penicillin	Inhibition of cell wall synthesis: Bactericidal	As for Penicillin G but also (β-lactamase producing bacteria	Superficial skin and systemic or deep Staphylococcal infections. Problem: about 40% of *S aureus* and > than 70% of coagulase negative staphylococci now resistant to the antibiotic	
Cephalexin	1st generation oral Cephalosporin (β-lactam)	Inhibition of cell wall synthesis: Bactericidal	Gram –ve (*E.coli, K. pneumoniae* & *P. mirabilis, Moraxella catarrhalis* –excellent) Gram +ve cocci (good but not drug of choice) Poor activity against H. influenzae. No activity against *Bacteroides fragilis*, enterococci, methicillin resistant staphylococci, *Pseudomonas, Acinebacter, Enterobacter*, indole positive Proteus.	Community acquired UTI mainly	
Cefotaxime (parenteral)	3rd generation Cephalosporin (β-lactam)	Inhibition of cell wall synthesis: Bactericidal	Mainly Gram-ve bacilli. Less active against Gram +ve particularly *Staph aureus*. Poor activity against *Pseudomonas*	Hospital acquired infections caused by multi resistant organisms e.g. Non-pseudomonal Hospital acquired pneumonia, bacterial meningitis, gonococcal infections, salmonellosis, typhoid fever	
Ceftriazone (parenteral)	3rd generation Cephalosporin (β-lactam)	Inhibition of cell wall synthesis: Bactericidal	Gram-ve bacilli (excellent) also S. pneumoniae and penicillin resistant Neisseria. Poor activity – Bacteroides. No activity methicillin resistant staphylococci, *Enterococcus, Acinebacter.*	Non-pseudomonal Hospital acquired pneumonia, bacterial meningitis, gonococcal infections, salmonellosis typhoid fever	
Cotrimoxazole (Sulphamethoxazole/Trimethoprim)	Sulphonamide/Diaminopyrimidine	Folate utilisation inhibitors Bactericidal	Gram –ve organism – E. coli, *Proteus* spp, *Klebsiella* spp. *H. influenzae, Moraxella catarrhalis, Acinetobacter, Yersinia enterocolitica, Enterobacter* spp, *Brucella abortus Salmonella* spp, *Serratia* spp, *Nocardia asteroides* etc and Gram +ve cocci – *S.*	Uncomplicated UTI (except UTI caused by enterococci- E. faecalis & E. faecium – common in the elderly) otitis media, URTI suspected to be caused by S. pneumoniae, H influenzae or M. catarrhalis; gonococcal and meningococcal infections,	

			pneumoniae, S. pyogenes, S. viridans, S. aureus, S. epidermidis, No activity against anaerobes.	chancroid	
Erythromycin	Macrolide	Inhibition of protein synthesis: Bactericidal	Gram + ve bacteria and also *Legionela, Mycoplasma, Campylobacter, Bortela pertusis* and some *Chlamydia*	Community acquired pneumonia, Streptococcal pharyngitis. Bacillary angiomatosis caused by Bartonella henselae in Immunocompromised patients	Incompatible with Chloramphenicol Both compete for same binding site on Bacterial 50S ribosomal unit
Doxycycline	Tetracycline	Inhibition of protein synthesis: Bacteriostatic	Broad spectrum (Gram +ve and Gram –ve bacteria, *Clamydia trachomatis*	Most community acquired infections including community acquired pneumonia, Chronic bronchitis, Brucellosis (with Rifampicin), Chlamydia, Mycoplasma and Rickettsia, pleural effusions; acne vulgaris; Chronic prostatitis & sinusitis. Tularaemia, Cholera, Unspecific urethritis (Clamydia trachomatis) STDs (Gonococcal infections Acute epididymitis (with Ceftriaxone) {No longer recommended for UTI: most enteric organisms responsible are now resistant)	Incompatible with bactericidal agents e.g. penicillins
Tetracycline	Tetracycline	Inhibition of protein synthesis: Bacteriostatic	Broad spectrum (Gram +ve and Gram –ve bacteria. *Clamydia trachomatis*	As above for Doxycycline	Incompatible with bactericidal agents e.g. penicillins
Chloramphenicol	Chloramphenicol	Inhibition of protein synthesis: Primarily Bacteriostatic . Bactericidal to H. influenzae, N. meningitides and S. pneumoniae	Broad spectrum (Gram +ve cocci inclusive of i- *S. pneumoniae, S. pyogenes, N. gonorrhoeae, N. meningitides* and Gram-ve bacilli including *H. influenzae, E.coli, K. pneumoniae,*& *Proteus* spp. *Pseudomonas aeruginosa* is completely resistant.	Typhoid fever and plague (Yersinia pestis) Brucellosis and pneumococcal and meningococcal meningitis in pats with Penicillin allergy	Incompatible with Erythromycin, Clindamycin and Lincomycin. Both drugs compete for same binding site on Bacterial 50S ribosomal unit
Ciprofloxacin	Fluoroquinolone	DNA gyrase & topoisomerase inhibitor: Bactericidal	Gram –ve bacilli (excellent) Gram +ve (variable) Greatest activity against *Pseudomonas* spp among	UTI, Community acquired pneumonia, bacterial gastroenteritis, enteric fever	Incompatible with penicillins

			oral agents.	(typhoid) Hospital acquired infections caused by Gram-ve organisms.	
Gentamicin	Aminoglycoside	Inhibition of protein synthesis: Inhibition of 30S ribosome: Bactericidal	Aerobic Gram-negative bacilli and staphylococci. Not effective against anaerobic bacteria.	Any suspected gram –ve bacteraemia infection, Staphylococcal, enterococcal or viridian enterococcal endocarditis in combination with Penicillins. Upper UTI Activity limited in abscess associated infections & Infections of CNS.	Synergistic with Penicillins
Amikacin	Aminoglycoside	Inhibition of protein synthesis: Bactericidal	Aerobic Gram-negative bacilli and staphylococci. Not effective against anaerobic bacteria.	Any suspected gram –ve bacteremic infection, Staphylococcal, enterococcal or viridian enterococcal endocarditis in combination with Penicillins. Upper UTI Activity limited in abscess associated infections & Infections of CNS.	Synergistic with Penicillins
Metronidazole	Imidazole	Electrophilic radical reactive destruction of bacterial DNA Bactericidal at therapeutic concentrations	Anaerobic pathogens (Gram +ve and Gram -ve): *Bacteroides, Clostridium* and *Helicobacter*	Abscesses involving obligate anaerobes e.g. lung, in brain and intra abdominal abscesses. Metronidazole + other antibacterial agents when facultative and aerobic pathogens are involved. abscesses, bacterial vaginosis & antibiotic associated pseudo membranous colitis	
Nalidixic acid	Quinolone	DNA gyrase & topoisomerase inhibitor: Bactericidal	Gram-negative bacteria causing UTI. *P. aeruginosa* resistant.	Lower Urinary tract infection	
Nitrofurantoin	Nitrofuran	Electrophilic radical reactive destruction of bacterial DNA Bactericidal at therapeutic concentrations	Gram-negative enteric bacteria	Lower Urinary tract infection	

Appendix 8

Data collection tool: 5 **Antibiotic prescription Data Summary tool for inpatient treatment cost determination.**

Study site _____

Rec No	Prescribed antibiotic/antibiotics	Discontinued during course of treatment?	Treatment Cost Determination									
			Cost of Antibiotics							Cost of Hospitalisation		
			Unit Dose	Unit doses/day	No of days administered	Total unit doses administered	Cost/ unit dose	Cost of given antibiotic course	Cost of all antibiotic courses used in treatment	No of days Hospitalised	Daily cost of hospital stay	Estimated cost of hospitalisation

Appendix 9

Data collection tool: 6 Antibiotic prescription Data Summary tool for Outpatient treatment cost determination

Study site _____

Rec no.	Prescribed antibiotic/anti biotics	Prescriber's 1st, 2nd, or 3rd choice?	Antibiotic Treatment Cost Determination						
			Unit Dose	Unit doses/day	No of days to be taken or given	Total unit doses to be taken or given	Cost/ unit dose	Cost of a prescribed antibiotic course	Total cost of prescribed antibiotics

Appendix 10

Data collection tool 7: Antibiotic cost data collection tool

Code	Name of Antibiotic	Formulation	Unit pack	Cost per unit pack
1	Amoxicillin	Caps		
2	Ampicillin	Caps		
3	Bactrim (Cotrimoxazole)	Tabs		
4	Cephalexin	Caps		
5	Chloramphenicol	Caps		
6	Ciprofloxacin	Tabs		
7	Cloxacillin	Caps		
8	Doxycycline	Tabs		
9	Erythromycin	Tabs		
10	Metronidazole	Tabs		
11	Nalidixic acid	Tabs		
12	Nitrofurantoin	Tabs		
13	Penicillin V	Tabs		
30	Tetracycline	Caps		
31	Ofloxacin	Tabs		
14	Amoxicillin	Suspension		
15	Ampicillin	Suspension		
16	Bactrim (Cotrimoxazole)	Suspension		
17	Chloramphenicol	Suspension		
18	Cloxacillin	Suspension		
19	Erythromycin	Suspension		
20	Metronidazole	Suspension		
21	Penicillin V	Suspension		
22	Amikacin	Injection		
23	Ampicillin	Injection		
24	Cefotaxime	Injection		
32	Benzathine Penicillin	Injection		
33	Ceftriazone	Injection		
25	Chloramphenicol	Injection		
26	Cloxacillin	Injection		
27	Flagyl	Infusion		
28	Gentamicin	Injection		
29	Penicillin G	Injection		
34	Procaine Penicillin	Injection		

Appendix 11

Data collection tool #8: Pathogen antibiotic culture sensitivity test results data collection form.

STUDY SITE: _____ Data Collection Period: From _____ To _____

Cultured Specimen _____ Year of Isolation _____ Month of Isolation _____

Bacterial pathogen isolates Pathogens	#	Amp		Peni		Eryth		Tetra		Chlor		Tri/Sul		Sulp		Met		Gen		Ami		Cipr		Cefot		Nali		Nitr	
		S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R
α-Haemolytic strept																													
β-Haemolytic strept																													
Non haemolytic strept																													
Staph aureus																													
Staph epidermidis																													
Neisseria spp																													
Enterobacter spp																													
Klebsiella spp																													
Proteus spp																													
H. influenzae																													
H. parainfluenzae																													
Pseudomonas spp																													
Acinebacter spp																													
Salmonella spp																													
Shigella spp																													
Bacteroides spp																													

Appendix 12: Calculated percentage overall activities (POA) of antibiotics against major pathogens associated with infections among inpatients and outpatients

Abbreviations used in tables [Tables 12(i) to 1(xiv)]

FI: Frequency of isolation; PFI: Percentage frequency of isolation; %S: Percentage sensitivity; $P_{(i)}$: Probability of isolation

P(s) Probability of pathogen sensitivity to antibiotic; $P_{(i)} \cap P_{(s)}$: Probability of pathogen isolation and its being sensitive to given antibiotic.

Appendix 12 (i) Percentage overall activity determinations of antibiotics against major pathogens associated with ascites among inpatients (Source of isolates: **Ascitic fluid** from inpatients)

Pathogen	FI	PFI	$P_{(i)}$	Probabilities of pathogen sensitivities to antibiotics and antibiotic activities against bacterial isolates ($P_{(i)} \cap P_{(s)}$)											
				Ampicillin			Co-trimoxazole			Tetracycline			Chloramphenicol		
				%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$
α-Haem strep (S. pneumoniae)	2	14.3	0.14	89.7	0.90	0.13	66.0	0.66	0.09	72.0	0.72	0.10	86.7	0.87	0.12
S. aureus	3	21.4	0.21	39.3	0.39	0.08	38.6	0.39	0.08	47.0	0.47	0.10	64.3	0.64	0.13
Escherichia coli	6	43.0	0.43	16.0	0.16	0.07	35.4	0.35	0.15	32.0	0.32	0.14	57.3	0.57	0.24
Klebsiella spp	3	21.4	0.21	17.5	0.18	0.04	31.7	0.31	0.07	37.0	0.37	0.08	53.4	0.53	0.11
Total	**14**	**100**	**0.99**			**0.32**			**0.39**			**0.42**			**0.60**
POA				**32.0**			**39.0**			**42.0**			**60.0**		

Pathogen	FI	PFI	$P_{(i)}$	Probabilities of pathogen sensitivities to antibiotics and antibiotic activities against bacterial isolates ($P_{(i)} \cap P_{(s)}$)											
				Ciprofloxacin			TGC(Cefotaxime)								
				%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$						
α-Haem strep (S .pneumonia)	2	14.3	0.14	80.0	0.80	0.11	75.0	0.75	0.11						
S .aureus	3	21.4	0.21	73.0	0.73	0.15	73.1	0.73	0.15						
Escherichia coli	6	43.0	0.43	78.0	0.78	0.34	88.3	0.88	0.38						
Klebsiella spp	3	21.4	0.21	74.0	0.74	0.16	49.0	0.49	0.10						
Total	**14**	**100**	**0.99**			**0.76**			**0.74**						
POA				**76.0**			**74.00**								

Appendix 12 (ii) Percentage overall activity determinations of antibiotics against major pathogens associated with CNS infections (meningitis) among inpatients (Source of isolates: **Cerebrospinal fluid** from inpatients)

Pathogen	FI	PFI	$P_{(i)}$	Probabilities of pathogen sensitivities to antibiotics and antibiotic activities against bacterial isolates ($P_{(i)} \cap P_{(s)}$)											
				Ampicillin			Co-trimoxazole			Tetracycline			Chloramphenicol		
				%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$
α-Haem strep *(S. pneumoniae)*	37	52.0	0.52	89.7	0.90	0.47	66.0	0.66	0.34	72.0	0.72	0.37	86.7	0.87	0.45
Neisseria spp	2	3.0	0.03	40.0	0.40	0.01	25.0	0.25	0.01	90.0	0.90	0.03	50.0	0.50	0.02
Non-Haem strep	5	7.0	0.07	71.0	0.71	0.05	32.1	0.32	0.02	51.0	0.51	0.04	73.8	0.74	0.05
Staphylococcus.aureus	4	6.0	0.06	39.3	0.39	0.02	38.6	0.39	0.02	47.0	0.47	0.03	64.3	0.64	0.04
Staphylococcus epidermidis	14	20.0	0.20	48.5	0.49	0.10	31.6	0.32	0.06	33.0	0.33	0.07	54.8	0.55	0.11
Escherichia coli	4	6.0	0.06	16.0	0.16	0.01	35.4	0.35	0.02	32.0	0.32	0.02	57.3	0.57	0.03
Klebsiella spp	1	1.0	0.01	17.5	0.18	0.00	31.7	0.32	0.00	37.0	0.37	0.00	53.4	0.53	0.01
Haemophilus influenzae	4	6.0	0.06	50	0.50	0.03	0.0	0.00	0.00	100	1.00	0.06	100	1.00	0.06
Total	**71**	**101**	**1.01**			**0.69**			**0.47**			**0.62**			**0.77**
POA				**69.0**			**47.0**			**62.0**			**77.0**		

Pathogen	FI	PFI	$P_{(i)}$	Probabilities of pathogen sensitivities to antibiotics and antibiotic activities against bacterial isolates ($P_{(i)} \cap P_{(s)}$)											
				Ciprofloxacin			TGC(Cefotaxime)								
				%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$
α-Haem strep(S. pneumonia)	37	52.0	0.52	80.0	0.80	0.42	75.0	0.75	0.39						
Neisseria spp	2	3.0	0.03	50.0	0.50	0.02	100.0	1.00	0.03						
Non-Haem strep	5	7.0	0.07	100.0	1.00	0.07	90.5	0.91	0.06						
Staphylococcus.aureus	4	6.0	0.06	73.0	0.73	0.04	73.1	0.73	0.04						
Staphylococcus epidermidis	14	20.0	0.20	83.0	0.83	0.17	69.2	0.69	0.14						
Escherichia coli	4	6.0	0.06	78.0	0.78	0.05	88.3	0.88	0.05						
Klebsiella spp	1	1.0	0.01	74.0	0.74	0.01	49.0	0.49	0.00						
Haemophilus influenzae	4	6.0	0.06	100	1.00	0.06	100	1.00	0.06						
Total	**71**	**101**	**1.01**			**0.84**			**0.77**						
POA				**84.0**			**77.7**								

Appendix 12 (iii): Percentage overall activity determinations of antibiotics against major pathogens associated with lower respiratory tract infections among inpatients (Source of isolates: **Pleural fluid** from inpatients)

Pathogen	FI	PFI	$P_{(i)}$	Probabilities of pathogen sensitivities to antibiotics and antibiotic activities against bacterial isolates ($P_{(i)} \cap P_{(s)}$)											
				Ampicillin			Co-trimoxazole			Tetracycline			Chloramphenicol		
				%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$
α-Haem strep *(S. pneumoniae)*	5	28.0	0.28	89.7	0.90	0.25	66.0	0.66	0.18	72.0	0.72	0.20	86.7	0.87	0.24
Non-Haem strep	2	11.0	0.11	71.0	0.71	0.08	32.1	0.32	0.04	51.0	0.51	0.06	73.8	0.74	0.08
S. aureus	6	33.0	0.33	39.3	0.39	0.13	38.6	0.39	0.13	47.0	0.47	0.16	64.3	0.64	0.21
Escherichia coli	3	17.0	0.17	16.0	0.16	0.03	35.4	0.35	0.06	32.0	0.32	0.05	57.3	0.57	0.10
Klebsiella spp	2	11.0	0.11	17.5	0.18	0.02	31.7	0.32	0.04	37.0	0.37	0.04	53.4	0.53	0.06
Total	**18**	**100**	**1.0**			**0.51**			**0.45**			**0.51**			**0.69**
POA				**51.0**			**45.0**			**51.0**			**69.0**		

Pathogen	FI	%FI	$P_{(i)}$	Probabilities of pathogen sensitivities to antibiotics and antibiotic activities against bacterial isolates ($P_{(i)} \cap P_{(s)}$)											
				Ciprofloxacin			TGC(Cefotaxime)								
				%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$
α-Haem strep(S. pneumonia)	5	28.0	0.28	80.0	0.80	0.22	75.0	0.75	0.21						
Non-Haem strep	2	11.0	0.11	100.0	1.00	0.11	90.5	0.91	0.10						
S .aureus	6	33.0	0.33	73.0	0.73	0.24	73.1	0.73	0.24						
Escherichia coli	3	17.0	0.17	78.0	0.78	0.13	88.3	0.88	0.15						
Klebsiella spp	2	11.0	0.11	74.0	0.74	0.08	49.0	0.49	0.05						
Total	**18**	**100**	**1.0**			**0.78**			**0.75**						
POA				**78.0**			**75.0**								

Appendix 12 (iv): Percentage overall activity determinations of antibiotics against major pathogens associated with respiratory tract infections among inpatients (Source of isolates: **Sputum** from inpatients)

Pathogen	FI	PFI	$P_{(I)}$	Probabilities of pathogen sensitivities to antibiotics and antibiotic activities against bacterial isolates ($P_{(I)} \cap P_{(S)}$)											
				Ampicillin			Co-trimoxazole			Tetracycline			Chloramphenicol		
				%S	$P_{(S)}$	$P_{(I)} \cap P_{(S)}$	%S	$P_{(S)}$	$P_{(I)} \cap P_{(S)}$	%S	$P_{(S)}$	$P_{(I)} \cap P_{(S)}$	%S	$P_{(S)}$	$P_{(I)} \cap P_{(S)}$
α-Haem strep *(S. pneumoniae)*	9	22	0.22	89.7	0.90	0.20	66.0	0.66	0.15	72.0	0.72	0.16	86.7	0.87	0.19
β-Haem strep(*S. pyogenes*)	4	9.7	0.097	81.0	0.81	0.08	20.5	0.21	0.02	56.0	0.56	0.05	42.1	0.42	0.04
Non-Haem strep	4	9.7	0.097	71.0	0.71	0.07	32.1	0.32	0.03	51.0	0.51	0.05	73.8	0.74	0.07
S.aureus	15	36.6	0.37	39.3	0.39	0.14	38.6	0.39	0.14	47.0	0.47	0.17	64.3	0.64	0.24
Staphylococcus epidermidis	2	4.9	0.05	48.5	0.49	0.02	31.6	0.32	0.02	33.0	0.33	0.02	54.8	0.55	0.03
Klebsiella spp	7	17.1	0.17	17.5	0.18	0.03	31.7	0.32	0.05	37.0	0.37	0.06	53.4	0.53	0.09
Total	**41**	**100**	**1.00**			**0.54**			**0.413**			**0.0.51**			**0.66**
POA				**54**			**41.3**			**51**			**66**		

Pathogen	FI	PFI	$P_{(I)}$	Probabilities of pathogen sensitivities to antibiotics and antibiotic activities against bacterial isolates ($P_{(I)} \cap P_{(S)}$)											
				Ciprofloxacin			TGC(Cefotaxime)								
				%S	$P_{(S)}$	$P_{(I)} \cap P_{(S)}$	%S	$P_{(S)}$	$P_{(I)} \cap P_{(S)}$	%S	$P_{(S)}$	$P_{(I)} \cap P_{(S)}$	%S	$P_{(S)}$	$P_{(I)} \cap P_{(S)}$
α-Haem strep(S.pneumonia)	9	22	0.22	80.0	0.80	0.18	75.0	0.75	0.17						
β-Haem strep(*S. pyogenes*)	4	9.7	0.097	100	1.00	0.10	81.8	0.82	0.08						
Non-Haem strep	4	9.7	0.097	100.0	1.00	0.10	90.5	0.91	0.09						
S.aureus	15	36.6	0.37	73.0	0.73	0.3	73.1	0.73	0.27						
Staphylococcus epidermidis	2	4.9	0.05	83.0	0.83	0.04	69.2	0.69	0.03						
Klebsiella spp	7	17.1	0.17	74.0	0.74	0.13	49.0	0.49	0.08						
Total	**41**	**100**	**1.00**			**0.85**			**0.72**						
POA				**85**			**72**								

Appendix 12 (v): Percentage overall activity determinations of antibiotics against major pathogens associated with **respiratory tract infections** in out patient department (Source of isolates: Modified list of isolates associated with sputum specimens from inpatients)

Pathogen	FI	PFI	$P_{(i)}$	Probabilities of pathogen sensitivities to antibiotics and antibiotic activities against bacterial isolates ($P_{(i)} \cap P_{(s)}$)											
				Ampicillin			Co-trimoxazole			Tetracycline			Chloramphenicol		
				%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$
α-Haem strep *(S. pneumoniae)*	9	24	0.24	89.7	0.90	0.22	66.0	0.66	0.16	72.0	0.72	0.17	86.7	0.87	0.21
β-Haem strep(*S. pyogenes*)	4	10.8	0.11	81.0	0.81	0.09	20.5	0.21	0.02	56.0	0.56	0.06	42.1	0.42	0.05
Staphylococcus aureus	15	40.5	0.41	39.3	0.39	0.16	38.6	0.39	0.16	47.0	0.47	0.19	64.3	0.64	0.26
Staphylococcus epidermidis	2	5.4	0.05	48.5	0.49	0.02	31.6	0.32	0.02	33.0	0.33	0.02	54.8	0.55	0.03
Klebsiella spp	7	18.9	0.19	17.5	0.18	0.03	31.7	0.32	0.06	37.0	0.37	0.07	53.4	0.53	0.10
Total	**37**	**100**	**1.00**			**0.52**			**0.42**			**0.51**			**0.65**
POA				**52**			**42**			**51**			**65**		

Pathogen	FI	PFI	$P_{(i)}$	Probabilities of pathogen sensitivities to antibiotics and antibiotic activities against bacterial isolates ($P_{(i)} \cap P_{(s)}$)											
				Ciprofloxacin			TGC(Cefotaxime)								
				%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$
α-Haem strep(S.pneumonia)	9	24	0.24	80.0	0.80	0.19	75.0	0.75	0.18						
β-Haem strep(*S. pyogenes*)	4	10.8	0.11	100	1.00	0.11	81.8	0.82	0.09						
S.aureus	15	40.5	0.41	73.0	0.73	0.30	73.1	0.73	0.30						
Staphylococcus epidermidis	2	5.4	0.05	83.0	0.83	0.04	69.2	0.69	0.03						
Klebsiella spp	7	18.9	0.19	74.0	0.74	0.14	49.0	0.49	0.09						
Total	**37**	**100**	**1.00**			**0.78**			**0.69**						
POA				**78**			**69**								

Appendix 12 (vi): Percentage overall activity determinations of antibiotics against major pathogens associated with throat infections among inpatients (Source of isolates: **Throat swab** from inpatients)

Pathogen	FI	PFI	$P_{(i)}$	Probabilities of pathogen sensitivities to antibiotics and antibiotic activities against bacterial isolates ($P_{(i)} \cap P_{(s)}$)											
				Ampicillin			Penicillin			Erythromycin			Co-trimoxazole		
				%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$
α-Haem strep *(S. pneumoniae)*	9	24.3	0.24	89.7	0.90	0.22	77.4	0.77	0.18	77.3	0.77	0.18	66.0	0.66	0.16
β-Haem strep *(S. pyogenes)*	9	24.3	0.24	81.0	0.81	0.19	60.5	0.61	0.15	60.7	0.61	0.15	20.5	0.21	0.05
Non-Haem strep	12	32.4	0.32	71.0	0.71	0.23	48.1	0.48	0.15	59.3	0.59	0.19	32.1	0.32	0.10
Staphylococcus.aureus	7	18.9	0.19	39.3	0.39	0.07	23.5	0.24	0.05	67.3	0.67	0.13	38.6	0.39	0.07
Total	**37**	**99.9**	**0.99**			**0.71**			**0.53**			**0.65**			**0.38**
%Overall activity				**71.0**			**53.0**			**65.0**			**38.0**		

Pathogen	FI	PFI	$P_{(i)}$	Probabilities of pathogen sensitivities to antibiotics and antibiotic activities against bacterial isolates ($P_{(i)} \cap P_{(s)}$)											
				Methicilin/Cloxacillin			Tetracycline			Chloramphenicol			Ciprofloxacin		
				%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$
α-Haem strep(S.pneumonia)	9	24.3	0.24	66.0	0.66	0.16	72.0	0.72	0.17	86.7	0.87	0.21	80.0	0.80	0.19
β-Haem strep *(S. pyogenes)*	9	24.3	0.24	80.0	0.80	0.19	56.0	0.56	0.13	42.1	0.42	0.10	100.0	1.00	0.24
Non-Haem strep	12	32.4	0.32	50.0	0.50	0.16	51.0	0.51	0.16	73.8	0.74	0.24	100.0	1.00	0.32
Staphylococcus.aureus	7	18.9	0.19	75.0	0.75	0.14	47.0	0.47	0.09	64.3	0.64	0.12	73.0	0.73	0.14
Total	**37**	**99.9**	**0.99**			**0.65**			**0.55**			**0.67**			**0.89**
POA				**65.0**			**55.0**			**67.0**			89.0		

Pathogen	FI	PFI	$P_{(i)}$	Probabilities of pathogen sensitivities to antibiotics and antibiotic activities against bacterial isolates ($P_{(i)} \cap P_{(s)}$)											
				TGC(Cefotaxime)											
				%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$									
α-Haem strep(S.pneumonia)	9	24.3	0.24	75.0	0.75	0.18									
β-Haem strep *(S. pyogenes)*	9	24.3	0.24	81.8	0.82	0.20									
Non-Haem strep	12	32.4	0.32	90.5	0.91	0.29									
Staphylococcus.aureus	7	18.9	0.19	73.1	0.73	0.14									
Total	**37**	**99.9**	**0.99**			**0.81**									
POA				**81.0**											

Appendix 12 (vii): Percentage overall activity determinations of antibiotics against major pathogens associated with throat infections among outpatients (Source of isolates: Modified list of isolates associated with **throat swab** from inpatients)

Pathogen	FI	PFI	$P_{(i)}$	Probabilities of pathogen sensitivities to antibiotics and antibiotic activities against bacterial isolates ($P_{(i)}\cap P_{(s)}$)											
				Ampicillin			Penicillin			Erythromycin			Co-trimoxazole		
				%S	$P_{(s)}$	$P_{(i)}\cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)}\cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)}\cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)}\cap P_{(s)}$
α-Haem strep *(S. pneumoniae)*	9	36.0	0.36	89.7	0.90	0.32	77.4	0.77	0.28	77.3	0.77	0.28	66.0	0.66	0.24
β-Haem strep *(S. pyogenes)*	9	36.0	0.36	81.0	0.81	0.29	60.5	0.61	0.22	60.7	0.61	0.22	20.5	0.21	0.08
Staphylococcus.aureus	7	28.0	0.28	39.3	0.39	0.11	23.5	0.24	0.07	67.3	0.67	0.19	38.6	0.39	0.11
Total	**25**	**100**	**0.99**			**0.72**			**0.57**			**0.69**			**0.43**
POA				**72.0**			**57.0**			**69.0**			**43.0**		

Pathogen	FI	PFI	$P_{(i)}$	Probabilities of pathogen sensitivities to antibiotics and antibiotic activities against bacterial isolates ($P_{(i)}\cap P_{(s)}$)											
				Methicilin/Cloxacillin			Tetracycline			Chloramphenicol			Ciprofloxacin		
				%S	$P_{(s)}$	$P_{(i)}\cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)}\cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)}\cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)}\cap P_{(s)}$
α-Haem strep(S. pneumoniae)	9	36.0	0.36	66.0	0.66	0.24	72.0	0.72	0.26	86.7	0.87	0.31	80.0	0.80	0.29
β-Haem strep *(S. pyogenes)*	9	36.0	0.36	80.0	0.80	0.29	56.0	0.56	0.20	42.1	0.42	0.15	100.0	1.00	0.36
Staphylococcus.aureus	7	28.0	0.28	75.0	0.75	0.21	47.0	0.47	0.14	64.3	0.64	0.18	73.0	0.73	0.20
Total	**25**	**100**	**0.99**			**0.74**			**0.60**			**0.64**			**0.85**
POA				**74.0**			**60.0**			**64.0**			**85.0**		

Pathogen	FI	PFI	$P_{(i)}$	Probabilities of pathogen sensitivities to antibiotics and antibiotic activities against bacterial isolates ($P_{(i)}\cap P_{(s)}$)											
				TGC(Cefotaxime)											
				%S	$P_{(s)}$	$P_{(i)}\cap P_{(s)}$									
α-Haem strep(S. pneumoniae)	9	36.0	0.36	75.0	0.75	0.27									
β-Haem strep *(S. pyogenes)*	9	36.0	0.36	81.8	0.82	0.30									
Staphylococcus.aureus	7	28.0	0.28	73.1	0.73	0.20									
Total	**25**	**100**	**0.99**			**0.77**									
POA				**77.0**											

Appendix 12 (viii): Percentage overall activity determinations of antibiotics against major pathogens associated with skin and soft tissue infections among inpatients (Source of isolates: **Pus swab** from inpatients)

Pathogen	FI	PFI	$P_{(i)}$	Probabilities of pathogen sensitivities to antibiotics and antibiotic activities against bacterial isolates ($P_{(i)} \cap P_{(s)}$)											
				Ampicillin			Co-trimoxazole			Tetracycline			Chloramphenicol		
				%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$
α-Haem strep *(S. pneumoniae)*	37	2.0	0.02	89.7	0.90	0.02	66.0	0.66	0.01	72.0	0.72	0.01	86.7	0.87	0.02
β-Haem strep(*S. pyogenes*)	82	3.0	0,03	81.0	0.81	0.02	20.5	0.21	0.01	56.0	0.56	0.02	42.1	0.42	0.01
Non-Haem strep	75	3.0	0.03	71.0	0.71	0.02	32.1	0.32	0.01	51.0	0.51	0.02	73.8	0.74	0.02
S.aureus	938	38.0	0.38	39.3	0.39	0.15	38.6	0.39	0.15	47.0	0.47	0.18	64.3	0.64	0.24
Staphylococcus epidermidis	57	2.0	0.02	48.5	0.49	0.01	31.6	0.32	0.01	33.0	0.33	0.01	54.8	0.55	0.01
Acinebacter spp	11	0.4	0.004	20.0	0.20	.001	9.09	0.09	0.00	33.0	0.33	0.00	16.7	0.17	0.00
Escherichia coli	411	17.0	0.17	16.0	0.16	0.03	35.4	0.35	0.06	32.0	0.32	0.05	57.3	0.57	0.10
Klebsiella spp	225	9.0	0.09	17.5	0.18	0.02	31.7	0.32	0.03	37.0	0.37	0.03	53.4	0.53	0.05
Pseudomonas spp	249	10.0	0.10	15.8	0.16	0.02	18.8	0.19	0.02	31.0	0.31	0.03	39.0	0.39	0.04
Proteus spp	394	16.0	0.16	28.0	0.28	0.04	23.5	0.24	0.04	19.0	0.19	0.03	47.5	0.48	0.08
Total	**2479**	**100**	**1.00**			**0.34**			**0.34**			**0.38**			**0.57**
POA				**34.0**			**34.0**			**38.0**			**57.0**		

Pathogen	FI	PFI	$P_{(i)}$	Probabilities of pathogen sensitivities to antibiotics and antibiotic activities against bacterial isolates ($P_{(i)} \cap P_{(s)}$)											
				Ciprofloxacin			TGC(Cefotaxime)								
				%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$
α-Haem strep(S.pneumonia)	37	2.0	0.02	80.0	0.80	0.02	75.0	0.75	0.02						
β-Haem strep(*S. pyogenes*)	82	3.0	0,03	100	1.00	0.03	81.8	0.82	0.02						
Non-Haem strep	75	3.0	0.03	100.0	1.00	0.03	90.5	0.91	0.03						
S.aureus	938	38.0	0.38	73.0	0.73	0.28	73.1	0.73	0.28						
Staphylococcus epidermidis	57	2.0	0.02	83.0	0.83	0.02	69.2	0.69	0.01						
Acinebacter spp	11	0.4	0.004	67.0	0.67	0.00	30.0	0.30	0.00						
Escherichia coli	411	17.0	0.17	78.0	0.78	0.13	88.3	0.88	0.15						
Klebsiella spp	225	9.0	0.09	74.0	0.74	0.07	49.0	0.49	0.04						
Pseudomonas spp	249	10.0	0.10	90.0	0.90	0.09	76.0	0.76	0.08						
Proteus spp	394	16.0	0.16	90.2	0.90	0.14	91.2	0.91	0.15						
Total	**2479**	**100**	**1.00**			**0.81**			**0.78**						
%Overall activity				**81.0**			**78.0**								

Appendix 12 (ix): Percentage overall activity determinations of antibiotics against major pathogens associated with skin and soft tissue infections among outpatients (Source of isolates: Modified list of isolates associated with **pus swab isolates** from inpatients)

Pathogen	FI	PFI	$P_{(i)}$	Probabilities of pathogen sensitivities to antibiotics and antibiotic activities against bacterial isolates ($P_{(i)} \cap P_{(s)}$)											
				Ampicillin			Co-trimoxazole			Penicillin			Erythromycin		
				%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$
α-Haem strep *(S. pneumoniae)*	37	3.1	0.03	89.7	0.90	0.03	66.0	0.66	0.02	60.5	0.61	0.02	60.7	0.61	0.02
β-Haem strep(*S. pyogenes*)	82	6.9	0,07	81.0	0.81	0.06	20.5	0.21	0.01	74.4	0.74	0.05	77.3	0.77	0.05
Non-Haem strep	75	6.3	0.06	71.0	0.71	0.04	32.1	0.32	0.02	48.1	0.48	0.03	59.3	0.59	0.04
S.aureus	938	78.9	0.79	39.3	0.39	0.31	38.6	0.39	0.31	23.5	0.24	0.19	67.3	0.67	0.53
Staphylococcus epidermidis	57	4.8	0.05	48.5	0.49	0.02	31.6	0.32	0.02	31.4	0.31	0.02	46.6	0.47	0.02
Total	**1189**	**100**	**1.00**			**0.46**			**0.38**			**0.31**			**0.66**
POA				**46.0**			**38.0**			**31**			**66**		

Pathogen	FI	PFI	$P_{(i)}$	Probabilities of pathogen sensitivities to antibiotics and antibiotic activities against bacterial isolates ($P_{(i)} \cap P_{(s)}$)											
				Tetracycline			Chloramphenicol			Ciprofloxacin			TGC(Cefotaxime)		
				%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	%S	%S	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$
α-Haem strep(S.pneumonia)	37	3.1	0.03	72.0	0.72	0.03	86.7	0.87	0.03	80.0	0.80	0.02	75.0	75.0	75.0
β-Haem strep(*S. pyogenes*)	82	6.9	0,07	56.0	0.56	0.04	42.1	0.42	0.03	100	1.00	0.07	81.8	81.8	81.8
Non-Haem strep	75	6.3	0.06	51.0	0.51	0.03	73.8	0.74	0.04	100.0	1.00	0.06	90.5	90.5	90.5
S.aureus	938	78.9	0.79	47.0	0.47	0.37	64.3	0.64	0.51	73.0	0.73	0.58	73.1	73.1	73.1
Staphylococcus epidermidis	57	4.8	0.05	33.0	0.33	0.02	54.8	0.55	0.03	83.0	0.83	0.04	69.2	69.2	69.2
Total	**1189**	**100**	**1.00**			**0.49**			**0.64**			**0.77**			**74.0**
POA				**49**			**64.0**			**77.0**			**74.0**		

Appendix 12 (x): Percentage overall activity determinations of antibiotics against major pathogens associated with ear infections among inpatients: ((Source of isolates: **Ear swab** from inpatients)

Pathogen	FI	PFI	$P_{(i)}$	Probabilities of pathogen sensitivities to antibiotics and antibiotic activities against bacterial isolates ($P_{(i)} \cap P_{(s)}$)											
				Ampicillin			Co-trimoxazole			Tetracycline			Chloramphenicol		
				%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$
α-Haem strep *(S. pneumoniae)*	5	2.0	0.02	89.7	0.90	0.02	66.0	0.66	0.01	72.0	0.72	0.01	86.7	0.87	0.02
Non-Haem strep	12	4.0	0.04	71.0	0.71	0.03	32.1	0.32	0.01	51.0	0.51	0.02	73.8	0.74	0.03
S.aureus	128	41.0	0.41	39.3	0.39	0.16	38.6	0.39	0.16	47.0	0.47	0.19	64.3	0.64	0.26
Staphylococcus epidermidis	8	3.0	0.03	48.5	0.49	0.01	31.6	0.32	0.01	33.0	0.33	0.01	54.8	0.55	0.02
Escherichia coli	20	6.0	0.06	16.0	0.16	0.01	35.4	0.35	0.02	32.0	0.32	0.02	57.3	0.57	0.03
Klebsiella spp	12	4.0	0.04	17.5	0.18	0.01	31.7	0.32	0.01	37.0	0.37	0.01	53.4	0.53	0.02
Pseudomonas spp	54	17.0	0.17	15.8	0.16	0.03	18.8	0.19	0.03	31.0	0.31	0.05	39.0	0.39	0.07
Proteus spp	69	22.0	0.22	28.0	0.28	0.06	23.5	0.24	0.05	19.0	0.19	0.04	47.5	0.47	0.10
Haemophilus influenzae	5	2.0	0.02	50.0	0.50	0.01	0.0	0.0	0.0	100	1.0	0.02	100	1.0	0.02
Total	**313**	**101**	**1.01**			**0.34**			**0.30**			**0.37**			**0.57**
POA				**34.0**			**30.0**			**37.0**			**57.0**		

Pathogen	FI	PFI	$P_{(i)}$	Probabilities of pathogen sensitivities to antibiotics and antibiotic activities against bacterial isolates ($P_{(i)} \cap P_{(s)}$)											
				Ciprofloxacin			TGC(Cefotaxime)								
				%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$
α-Haem strep(S.pneumonia)	5	2.0	0.02	80.0	0.80	0.02	75.0	0.75	0.02						
Non-Haem strep	12	4.0	0.04	100.0	1.00	0.04	90.5	0.91	0.04						
S.aureus	128	41.0	0.41	73.0	0.73	0.30	73.1	0.73	0.30						
Staphylococcus epidermidis	8	3.0	0.03	83.0	0.83	0.02	69.2	0.69	0.02						
Escherichia coli	20	6.0	0.06	78.0	0.78	0.05	88.3	0.88	0.05						
Klebsiella spp	12	4.0	0.04	74.0	0.74	0.03	49.0	0.49	0.02						
Pseudomonas spp	54	17.0	0.17	90.0	0.90	0.15	76.0	0.76	0.13						
Proteus spp	69	22.0	0.22	90.2	0.90	0.20	91.2	0.91	0.20						
Haemophilus influenzae	5	2.0	0.02	100.0	1.0	0.02	100	1.0	0.02						
Total	**313**	**101**	**1.01**			**0.83**			**0.80**						
POA				**83.0**			**80.0**								

Appendix 12 (xi): Percentage overall activity determinations of antibiotics against major pathogens associated with ear infections in outpatient department (Source of isolates: Modified list of isolates associated with **ear swab** specimens from inpatients)

Pathogen	FI	PFI	$P_{(i)}$	Probabilities of pathogen sensitivities to antibiotics and antibiotic activities against bacterial isolates ($P_{(i)} \cap P_{(s)}$)											
				Ampicillin			Co-trimoxazole			Tetracycline			Chloramphenicol		
				%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$
α-Haem strep *(S. pneumoniae)*	5	2.5	0.03	89.7	0.90	0.03	66.0	0.66	0.02	72.0	0.72	0.02	86.7	0.87	0.03
S.aureus	128	64	0.64	39.3	0.39	0.25	38.6	0.39	0.25	47.0	0.47	0.30	64.3	0.64	0.41
Staphylococcus epidermidis	8	4.0	0.04	48.5	0.49	0.02	31.6	0.32	0.01	33.0	0.33	0.01	54.8	0.55	0.02
Pseudomonas spp	54	27.0	0.27	15.8	0.16	0.04	18.8	0.19	0.05	31.0	0.31	0.08	39.0	0.39	0.11
Haemophilus influenzae	5	2.5	0.03	50.0	0.50	0.02	0.0	0.0	0.0	100	1.0	0.03	100	1.0	0.03
Total	**200**	**101**	**1.01**			**0.36**			**0.33**			**0.44**			**0.60**
POA				**36.0**			**33.0**			**44.0**			**60.0**		

Pathogen	FI	PFI	$P_{(i)}$	Probabilities of pathogen sensitivities to antibiotics and antibiotic activities against bacterial isolates ($P_{(i)} \cap P_{(s)}$)											
				Ciprofloxacin			TGC(Cefotaxime)								
				%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$
α-Haem strep(S.pneumonia)	5	2.5	0.03	80.0	0.80	0.02	75.0	0.75	0.02						
S.aureus	128	64	0.64	73.0	0.73	0.45	73.1	0.73	0.47						
Staphylococcus epidermidis	8	4.0	0.04	83.0	0.83	0.03	69.2	0.69	0.03						
Pseudomonas spp	54	27.0	0.27	90.0	0.90	0.24	76.0	0.76	0.21						
Haemophilus influenzae	5	2.5	0.03	100.0	1.0	0.03	100	1.0	0.03						
Total	**200**	**101**	**1.01**			**0.77**			**0.76**						
%Overall activity				**77.0**			**76.0**								

Appendix 12 (xii): Percentage overall activity determinations of antibiotics against major pathogens associated with urinary tract infections among inpatients:(Source of isolates: **urine specimen** from inpatients)

Pathogen	FI	PFI	$P_{(i)}$	Probabilities of pathogen sensitivities to antibiotics and antibiotic activities against bacterial isolates ($P_{(i)}\cap P_{(s)}$)											
				Ampicillin			Co-trimoxazole			Tetracycline			Chloramphenicol		
				%S	$P_{(s)}$	$P_{(i)}\cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)}\cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)}\cap P_{(s}$	%S	$P_{(s)}$	$P_{(i)}\cap P_{(s)}$
Non-Haem strep	40	2.4	0.024	71.0	0.71	0.017	32.1	0.32	0.008	51.0	0.51	0.01	73.8	0.74	0.01
β-Haem strept (S. pyogenes	40	2.4	0.024	81.0	0.81	0.019	20.5	0.21	0.005	56.0	0.56	0.013	42.1	0.42	0.01
Escherichia coli	1262	75.5	0.755	16.0	0.16	0.121	35.4	0.35	0.260	32.0	0.32	0.24	57.3	0.57	0.43
Klebsiella spp	236	14.1	0.141	17.5	0.18	0.025	32.0	0.32	0.045	37.0	0.37	0.05	53.4	0.53	0.07
Proteus spp	71	4.2	0.042	28.0	0.28	0.012	23.5	0.24	0.010	19.0	0.19	0.03	47.5	0.48	0.07
Pseudomonas spp	23	1.4	0.014	15.8	0.16	0.002	18.8	0.19	0.003	31.0	0.31	0.004	39.0	0.39	.005
Total	**1672**	**100**	**1.00**			**0.196**			**0.32**			**0.35**			**0.595**
POA				**19.6**			**32.0**			**35.0**			**59.5**		

%FI

Pathogen	FI	PFI	$P_{(i)}$	Probabilities of pathogen sensitivities to antibiotics and antibiotic activities against bacterial isolates ($P_{(i)}\cap P_{(s)}$)											
				Ciprofloxacin			TGC(Cefotaxime)								
				%S	$P_{(s)}$	$P_{(i)}\cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)}\cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)}\cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)}\cap P_{(s)}$
Non-Haem strep	40	2.4	0.024	100.0	1.00	0.02	90.5	0.91	0.02						
β-Haem strept(S. pyogenes)	40	2.4	0.024	80	0.80	0.02	75	0.75	0.02						
Escherichia coli	1262	75.5	0.755	78	0.78	0.59	88	0.88	0.66						
Klebsiella spp	236	14.1	0.141	74	0.74	0.10	49	0.49	0.07						
Proteus spp	71	4.2	0.042	90	0.90	0.04	76	0.76	0.03						
Pseudomonas spp	23	1.4	0.014	90.0	0.90	0.13	91.2	0.91	0.13						
Total	**1672**	**100**	**1.00**			**0.90**			**0.93**						
POA				**90.0**			**93.0**								

Appendix 12 (xiii): Percentage overall activity determinations of antibiotics against major pathogens associated with urinary tract infections among outpatients: (Source of isolates: Modified list of isolates associated with **urine specimens** of inpatients)

Pathogen	FI	PFI	$P_{(i)}$	Probabilities of pathogen sensitivities to antibiotics and antibiotic activities against bacterial isolates ($P_{(i)} \cap P_{(s)}$)											
				Ampicillin			Co-trimoxazole			Tetracycline			Chloramphenicol		
				%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$
β-Haem strept (S. pyogenes	40	2.5	0.03	81.0	0.81	0.02	20.5	0.21	0.01	56.0	0.56	0.02	42.1	0.42	0.01
Escherichia coli	1262	78.4	0.78	16.0	0.16	0.12	35.4	0.35	0.27	32.0	0.32	0.25	57.3	0.57	0.43
Klebsiella spp	236	14.7	0.15	17.5	0.18	0.03	32.0	0.32	0.05	37.0	0.37	0.06	53.4	0.53	0.07
Proteus spp	71	4.4	0.04	28.0	0.28	0.01	23.5	0.24	0.01	19.0	0.19	0.01	47.5	0.48	0.07
Total	**1609**	**100**	**1.00**			**0.18**			**0.34**			**0.34**			**0.595**
%Overall activity				**18.0**			**34.0**			**34.0**			**59.5**		

Pathogen	FI	PFI	$P_{(i)}$	Probabilities of pathogen sensitivities to antibiotics and antibiotic activities against bacterial isolates ($P_{(i)} \cap P_{(s)}$)											
				Ciprofloxacin			TGC(Cefotaxime)								
				%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$
β-Haem strept(S. pyogenes)	40	2.5	0.03	80	0.80	0.02	75	0.75	0.02						
Escherichia coli	1262	78.4	0.78	78	0.78	0.61	88	0.88	0.67						
Klebsiella spp	236	14.7	0.15	74	0.74	0.11	49	0.49	0.07						
Proteus spp	71	4.4	0.04	90	0.90	0.04	76	0.76	0.03						
Total	**1609**	**100**	**1.00**			**0.78**			**0.79**						
%Overall activity				**78.0**			**79**								

Appendix 12(xiv): Percentage overall activity determinations of antibiotics against major pathogens associated with genitourinary tract infections among inpatients: (Source of isolates: **High vaginal swab specimen** from inpatients)

Pathogen	FI	PFI	$P_{(i)}$	Probabilities of pathogen sensitivities to antibiotics and antibiotic activities against bacterial isolates ($P_{(i)} \cap P_{(s)}$)											
				Ampicillin			Co-trimoxazole			Tetracycline			Chloramphenicol		
				%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$
α-Haem strep *(S. pneumoniae)*	2	1.0	0.01	89.7	0.90	0.01	66.0	0.66	0.01	72.0	0.72	0.01	86.7	0.87	0.01
β-Haem strep(*S. pyogenes*)	7	3.0	0.03	81.0	0.81	0.02	20.5	0.21	0.01	56.0	0.56	0.02	42.1	0.42	0.01
Non-Haem strep	7	3.0	0.03	71.0	0.71	0.02	32.1	0.32	0.01	51.0	0.51	0.02	73.8	0.74	0.02
S.aureus	157	64.0	0.64	39.3	0.39	0.25	38.6	0.39	0.25	47.0	0.47	0.29	64.3	0.64	0.40
Staphylococcus epidermidis	4	2.0	0.02	48.5	0.49	0.01	31.6	0.32	0.01	33.0	0.33	0.01	54.8	0.55	0.01
Neisseria spp	4	2.0	0.02	40.0	0.40	0.01	25.0	0.25	0.01	90.0	0.90	0.02	50.0	0.50	0.01
Escherichia coli	36	15.0	0.15	16.0	0.16	0.02	35.4	0.35	0.05	32.0	0.32	0.04	57.3	0.57	0.09
Klebsiella spp	18	7.0	0.07	17.5	0.18	0.01	31.7	0.32	0.02	37.0	0.37	0.03	53.4	0.53	0.04
Proteus spp	12	5.0	0.05	28.0	0.28	0.01	23.5	0.24	0.01	19.0	0.19	0.01	47.5	0.48	0.02
Total	**247**	**102**	**1.02**			**0.36**			**0.36**			**0.43**			**0.61**
POA				**36.0**			**36.0**			**43.0**			**61.0**		

Pathogen	FI	PFI	$P_{(i)}$	Probabilities of pathogen sensitivities to antibiotics and antibiotic activities against bacterial isolates ($P_{(i)} \cap P_{(s)}$)											
				Ciprofloxacin			TGC(Cefotaxime)								
				%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$	%S	$P_{(s)}$	$P_{(i)} \cap P_{(s)}$
α-Haem strep(S.pneumonia)	2	1.0	0.01	80.0	0.80	0.01	75.0	0.75	0.01						
β-Haem strep(*S. pyogenes*)	7	3.0	0.03	100	1.00	0.03	81.8	0.82	0.02						
Non-Haem strep	7	3.0	0.03	100.	1.00	0.03	90.5	0.91	0.03						
S.aureus	157	64.0	0.64	73.0	0.73	0.47	73.1	0.73	0.45						
Staphylococcus epidermidis	4	2.0	0.02	67.0	0.67	0.01	30.0	0.30	0.01						
Neisseria spp	4	2.0	0.02	50.0	0.50	0.01	100.0	1.0	0.02						
Escherichia coli	36	15.0	0.15	78.0	0.78	0.12	88.3	0.88	0.12						
Klebsiella spp	18	7.0	0.07	74.0	0.74	0.05	49.0	0.49	0.03						
Proteus spp	12	5.0	0.05	90.2	0.90	0.05	91.2	0.91	0.05						
Total	**247**	**102**	**1.02**			**78.0**			**0.74**						
POA				**78.0**			**74.0**								

Appendix 13: Costs of treatment courses of formulary of antibiotics as of June 2006

Code	Name of Antibiotic	Formulation	Unit Pack	Cost of Unit pack (M)	Unit dose	Cost of Unit dose (Maloti)	Prescribed Unit doses per day	Prescribed no. of days of use (Outpatients)	Daily treatment Cost (M)	Cost of course of treatment (M)
	Oral Preparations									
1	Amoxycillin 250 mg	Caps	1000	232.00	500mg	0.46	3	7	1.38	9.66
32	Amoxy/Clav 250/125mg	Tabs	100	295.06	250/125mg	2.95	3	5	8.85	44.25
2	Ampicillin 250 mg	Caps	1000	203.04	500mg	0.40	4	7	1.60	11.20
3	Bactrim (Cotrimoxazole)400/80 mg	Tabs	1000	63.87	800/160mg	0.12	2	5	0.24	1.20
4	Cephalexin	Caps	1000							
5	Chloramphenicol	Caps	1000	154.96	500mg	0.16	4	7	0.64	4.48
6	Ciprofloxacin	Tabs	100	84.88	500mg	0.85	2	5	1.70	8.50
7	Cloxacillin	Caps	1000	187.44	500mg	0.38	4	7	1.52	6.08
8	Doxycycline 100mg	Tabs	1000	80.04	100mg	0,08	2 start then1dly	7	0.09	0.64
9	Erythromycin 250 mg	Tabs	1000	348.01	500mg	0.70	4	7	2.80	19.60
10	Metronidazole 200mg	Tabs	1000	29.98	400mg	0.03	3	10	0,09	0.90
11	Nalidixic acid 500mg	Tabs	500	710.87	1g	2.84	4	7	11.36	79.52
12	Nitrofurantoin 100mg	Tabs	1000	76.98	100mg	0.08	3	7	0.24	1.68
13	Penicillin V 250 mg	Tabs	1000	124.99	500mg	0.26	4	7	1.04	7.28
30	Tetracycline	Caps	1000	73.08	500mg	0.07	4	7	0.28	1.96
31	Ofloxacin	Tabs	1000							
14	Amoxicillin 125mg/5ml	Susp	100ml	4.08	125mg/5ml	0.20	4	5	0.80	4.00
15	Ampicillin 125mg/5ml	Susp	100ml	4.00	125mg/5ml	0.20	4	5	0.80	4.00
16	Bactrim (Cotrimoxazole) 40/8 mg/5ml	Susp	100ml	4.21	40/8mg/5ml	0.21	2	5	0.42	2.10
17	Chloramphenicol 125mg/5ml	Susp	100ml	5.75	125mg/5ml	0.29	4	5	1.16	5.80
18	Cloxacillin 125mg/5ml	Susp	100ml	4.94	125mg/5ml	0.25	4	5	1.00	5.00
19	Erythromycin 125mg/5ml	Susp	100ml	6.58	125mg/5ml	0.33	4	5	1.32	6.60
20	Metronidazole 200 mg /5ml	Susp	100ml	4.20	125mg/5ml	0.21	4	5	0.84	4.20
21	Penicillin V 125mg/5ml	Susp	100ml	4.09	125mg/5ml	0.20	4	5	0.80	4.00
	Parenteral Preparations									
22	Amikacin	Inj.	10s (amps)	37.00	500mg//2ml	3.7	2	N/A	6.40	N/A
23	Ampicillin	Inj.	50s (Vials)	34.19	500mg	0.68	4	N/A	2.72	N/A
24	Cefotaxime	Inj.	1s (Vials)	8.4 0	1g	8.40	2	N/A	17.80	N/A
33	Ceftriazone	Inj.	1s (vials)	8.50	1g	8.50	2	N/A	17.00	N/A
25	Chloramphenicol	Inj.	50s	84.63	1gm	1.70	4	N/A	6.80	N/A
26	Cloxacillin	Inj.	250mg	211.02	500mg	4.22	4	N/A	16.88	N/A
27	Flagyl	Inj.	1s (Vials)	7.47	500/100ml	7.47	3	N/A	22.41	N/A
28	Gentamicin	Inj.	100s (amps)	59.22	80mg	0.60	2	N/A	1.20	N/A
29	Penicillin G	Inj.	50s (vials)	250.61	5MU	5.01	4	N/A	20.04	N/A

Appendix 14

Questionnaires for investigating factors contributing to patterns of antibiotic prescribing at study sites.

Questionnaire number ☐

Name of Health Service area ☐
Location of Practice: Urban ☐
Rural ☐

QUESTIONS

Part I

1. Please indicate your qualification by ticking any of the following

i.	Physician Specialist/Consultant	☐ 1
ii.	Surgical Consultant	☐ 2
iii.	General Medical Practitioner	☐ 3
iv.	Nurse clinician	☐ 4
v.	Registered Nurse	☐ 5
vi.	Nursing assistant	☐ 6

2. For how long have you been in practice after your qualification?

i.	Equal to or less than 5 years	☐ 1
ii.	6-10yrs	☐ 2
iii.	More than 10 years	☐ 3

3. With respect to your practice type, which of the following applies to you

i.	Practice in a Government owned hospital	☐ 1
ii.	Practice in a CHAL hospital	☐ 2
iii.	Practice in both Private Clinic and either Govt or CHAL Hosp	☐ 3

4. Does your practice facility have a microbiology laboratory? Yes ☐ 1
No ☐ 2

If your answer to question 4 is "Yes", then please answer questions 5 & 6

5. **Does the microbiology laboratory in your facility perform culture sensitivity tests?**

Yes ☐ 1 No ☐ 2

6. **Does the microbiology laboratory in your facility routinely provide information on morphological characteristics (shape and grams stain) of bacteria when you request for them?**

YES ☐ 1 NO ☐ 2

7. **Which type of patients do you mainly manage?**

Outpatients ☐ 1 Inpatients ☐ 2 Both ☐ 3

8 **By way of quantifying your work load please indicate how many patients you see in a day on the average**

1-25 patients on the average a day ☐ 1
26 – 100 patients on the average a day ☐ 2
Over 100 patients on the average a day ☐ 3

Part II

9. **To what degree does any of the following factors influence your decision to prescribe Antibiotics?**

i. Clinical condition of patient i.e. biomedical factors.

Not at all ☐ 1 Minor degree ☐ 2 Major degree ☐ 3

ii. Quest to satisfy patients' request for an antibiotic.

Not at all ☐ 1 Minor degree ☐ 2 Major degree ☐ 3

iii. Quest to satisfy patients' expectations regarding what treatment they think they should be given for their presenting ailment

Not at all ☐ 1 Minor degree ☐ 2 Major degree ☐ 3

iv. Quest to eliminate an underlying infection of suspect in cases of unclear diagnosis.

Not at all ☐ 1 Minor degree ☐ 2 Major degree ☐ 3

v. Quest to prevent an infection even if I rule out the presence of bacterial infection.

Not at all ☐ 1 Minor degree ☐ 2 Major degree ☐ 3

vi. Past experience with this type of clinical condition

Not at all ☐ 1 Minor degree ☐ 2 Major degree ☐ 3

Part III

10. **If you prescribe in an out-patient setting please answer the following. How often would you do what the following statements imply?**

i. I prescribe antibiotics when the patient's presenting signs and symptoms make me suspect the presence of an infection.
Never ☐ 1 Sometimes ☐ 2 Always ☐ 3

ii. I prescribe antibiotics ONLY after I have examined a patient and my clinical findings positively establish the presence of an infection.
Never ☐ 1 Sometimes ☐ 2 Always ☐ 3

iii. I prescribe antibiotics ONLY after laboratory investigations have established the presence of infection.
Never ☐ 1 Sometimes ☐ 2 Always ☐ 3

iv. I prescribe antibiotics sometimes even if I am not sure of my diagnosis.
Never ☐ 1 Sometimes ☐ 2 Always ☐ 3

Part IV

11. **If you prescribe in an in-patient setting where facilities exist for you to perform culture sensitivity tests, please answer the following. What do you normally do in the course prescribing an antibiotic?**

i. Send a specimen to the microbiology laboratory for a rapid microscopic identification of infecting organisms and their grams stain properties before starting antibiotic treatment.

Yes ☐ 1 No ☐ 2 At times ☐ 3

ii. Send a specimen to the microbiology lab for culture sensitivity test before initiating empiric antibiotic therapy.

Yes ☐ 1 No ☐ 2 At times ☐ 3

iii. Start antibiotic treatment, monitor patient for response and later send specimen to the microbiology lab for culture sensitivity test only in the event of patient non response.

Yes ☐ 1 No ☐ 2 At times ☐ 3

iv. Revise antibiotic treatment by discontinuing initially prescribed antibiotics and replacing them with antibiotics to which organisms show sensitivity.

Yes ☐ 1 No ☐ 2 At times ☐ 3

v. Revise antibiotic treatment by adding antibiotics to which organisms are sensitive to initially prescribed antibiotics

Yes ☐ 1 No ☐ 2 At times ☐ 3

Part V

12. Indicate whether you agree or disagree with the following statement

In deciding to prescribe an antibiotic for the treatment of an infection it is necessary to identify at least one clinical sign as a hallmark of infection in the patient.

Agree ☐ 1 Disagree ☐ 2

13. Please indicate signs and hallmarks of an infection you consider necessary as guiding principles in prescribing antibiotics in the clinical conditions listed below.

i. Upper respiratory tract infection _____

ii. Lower respiratory tract infection _____

iii. Non sexually transmitted Urinary tract infection _____

14. Pyrexia as a clinical sign in a patient always justifies the prescription of an antibiotic.

Agree ☐ 1 Disagree ☐ 2

15. If your answer to question 13 above is "Disagree", please indicate which other possible clinical conditions may cause pyrexia in a patient to necessitate further investigation before the prescription of an antibiotic. _____

_____

Part V

16. To what degree do you consider the following factors when deciding to prescribe an antibiotic for a patient.

i. Knowledge of bacterial morphology and Gram's stain results

Not at all ☐ 1 Minor degree ☐ 2 Major degree ☐ 3

ii. Site of infection

Not at all ☐ 1 Minor degree ☐ 2 Major degree ☐ 3

iii. Patient factors e.g. allergic responses or side-effects to certain antibiotics

Not at all ☐ 1 Minor degree ☐ 2 Major degree ☐ 3

17. **Please indicate in each of the cases below which microbes or class of microbes are most likely to be target pathogens for antibiotic prescription.**

i. Upper respiratory tract infection _____

ii. Lower respiratory tract infection _____

iii. Non sexually transmitted Urinary tract infection _____

18. **Gram-positive cocci bacteria have been isolated from an infected surgical wound of a patient. Please indicate which of the following available antibiotics you will preferably prescribe empirically for this patient pending CST results**

i. Ampicillin ☐ 1

ii. Cotrimoxazole ☐ 2

iii. Cefotaxime (Claforan) ☐ 3

iv. Not sure of which of the above to use ☐ 4

v. Other (please specify) _____

19. **Gram-negative aerobic bacilli have been isolated from an infected surgical wound of a patient. Please indicate which of the following commonly available antibiotics you will prescribe for an empirical treatment of this infection.**

i. Ampicillin ☐ 1

ii. Cotrimoxazole ☐ 2

iii. Cefotaxime (Claforan) ☐ 3

iv. Not sure of which of the above to use ☐ 4

v. Other (please specify) _____

Part VI

20. **To what degree would you say the following factors served as guiding principles in your decision to select your antibiotic of choice in questions 18 and 19?**

i. Cost of antibiotic
Not at all ☐ 1 Minor degree ☐ 2 Major degree ☐ 3

ii. Degree of sensitivity of most likely bacterial isolate to antibiotic of choice
Not at all ☐ 1 Minor degree ☐ 2 Major degree ☐ 3

iii. Other (Specify) _____

21. **To what degree do you think unavailability of certain antibiotics in stock in your Pharmacy is a problem that limits your ability to select a given antibiotic in treating particular cases of infection?**

Not at all ☐ 1 Minor degree ☐ 2 Major degree ☐ 3

22. **If antibiotic stock outs become a problem what alternative measures do you take when it occurs to ensure effective patient management?**

i. Direct that patient buys antibiotic of my first choice from a retail Pharmacy

Yes ☐ 1 No ☐ 2

ii. Prescribe my second choice antibiotic which is available in the Pharmacy

Yes ☐ 1 No ☐ 2

Part VII

Please answer questions 23 to 25 if you practice in a clinical setting where there is a microbiology laboratory for pathogen identification and culture sensitivity determinations

23. **Do you request for microscopic identification or Gram's stain characteristics of bacterial pathogens causing an infection as routine or at least sometimes before initiating empiric antibiotic therapy?**

Yes ☐ 1 No ☐ 2

24. **If YES how long does it take for the results of such laboratory tests to be made available to you?**

i. Within 3 hours ☐ 1

ii. From 4 to 8 hours ☐ 2

iii. More than 8 hours ☐ 3

iv. Results are hardly received before prescription is made ☐ 4

25. **If NO provide a reason why you don't normally request for such information before deciding which antibiotic to use in presenting infection**

i. It is simply not feasible in my practice environment because of the large number of patients that have to be seen in the consulting room everyday ☐ 1

ii. My clinical experience is enough to guide me in what antibiotic to use in a presenting case of infection. ☐ 2

iii. In my opinion this is not cost-effective in patient management ☐ 3

iv. I don't because my experience has shown that even if I do the results will not be made available to me within a short enough time interval in time to enable me to base my choice of antibiotic on this information. ☐ 4

v. Other (Please specify) _____ ☐ 5

Part VIII

26. Do you think the provision of prescribing guidelines in the management of infections will help you in selecting antibiotics?

Yes ☐ 1 No ☐ 2

27. How would you grade your need for a refresher course on guiding principles in antibiotic prescription?

Don't need it ☐ 1 Need it ☐ 2 Need it very much ☐ 3

Part divisions of questionnaire and their objectives

Part I
Particulars of prescribers and their practice environments. (Questions 1-8)

Part II
Investigating the degree to which patient- and prescriber-related factors influence prescribers' decisions in the prescription of antibiotics. (Question 9)

Part III
Investigating prescriber habits in the prescription of antibiotics in out patient departments (Question 10)

Part IV
Investigating degree to which principles of rational antibiotic prescribing are adhered to in the prescription of antibiotics for inpatients.(Question 11)

Part V
Assessing prescribers' knowledge in the principles of rational antibiotic selection and prescribing and the determination of an association of lack of such knowledge and inappropriate prescribing of antibiotics (Questions 12 – 19.)

Part VI
Investigating major factors that prescribers' consider when they select and prescribe a given antibiotic from a group of available antibiotics. (Questions 20 – 22)

Part VII
Determining laboratory- and prescriber-related factors that explain failure on the part of prescribers to prescribe antibiotics empirically based on available information on the morphological characteristics of target organisms. (Questions 23 – 25)

Part VII
Collecting opinions of prescribers on their need for refresher courses and antibiotic prescription guidelines for the appropriate prescription of antibiotics in public health institutions in Lesotho.

Appendix 15: Marking scheme for questions testing knowledge (12 -19)

12. (1) Agree [1 mark]

13(i) **Acute sinusitis** : nasal purulence, congestion or cough for >7days, (adults) or for 10 -14 days in chn or focal facial swelling or tooth pain (adults or facial swelling or pain with fever (.102°F) (chn) lasting for any length of period
Acute pharyngitis/retropharyngeal abscess: Fever, tosilar swelling, exudates, enlarged/tender anterior cervical swelling lymph nodes, absence of cough or coryza,dysphagia or neck pain
Acute otitis media: Fluid in mid ear evidenced by purulent otorrhoea + Fever, irritability, otalgia, decreased hearing, tinnitus and vertigo infections of deep neck structures:
Epiglottitis: Enlarged cherry red looking epiglottis with fever, sore throat tachycardia, inspiratory stridor with muffled voice [3 marks for any 3]

13 (ii) Exacerbated Chronic **bronchitis**: Increased production of purulent sputum,
Pneumonia (Community or Hospital acquired): Fever, tachypnea, tarchycardia, pleuritic (knife like) chest pain, Dullness on chest percussion. Decreased breath sounds, vowel tone changes [3 marks for any 3]

13 (iii) Lower UTI : **Cystitis/**: Dysuria, frequent urination, suprabubic pain, grossly cloudy urine **Urithritis** which may be bloody
Upper UTI: **Acute pyelonephritis** : rapidly developing pain in the loin, fever, chills, nausea, vomiting and haematuria **Prostatitis**: Sudden onset of chills and fever, perineal and low back pain, urinary urgency and frequency; nocturia, dysuria, generalised malaise & prostration. [3 marks for 3]

14. (2) Disagree [1 mark]

15. Viral infections, some protozoal infections, neoplastic and autoimmune disorders[1 mark]

16(i) (3) major degree[1 mark]
16(i) (3) major degree[1 mark]
16(i) (3) major degree[1 mark]

17(i) Streptococci (*S. pneumoniae, S. pyogenes) H. influenzae, Moraxela catarrhalis (Gram-ve cocci) (Gram-ve bacilli) Corynebacterium diphtheriae (Gram-ve bacilli)* (Pharyngitis, Laryngitis, otitis media, epiglotitis) [2 marks for any 2]

17(ii) Streptococci (*S. pneumoniae, S. pyogenes Moraxella catarrhalis* (Gram-negative cocci) *Corynebacterium diphtheriae (Gram +ve bacilli) H. influenzae, Klebsiella pneumoniae, Pseudomonas aeruginosa (Gram -ve bacilli) Chlamydia pneumoniae and Pneumocystis carinii* [2 marks for any 2]

17(iii) Gram-negative bacilli (*E. coli*, Proteus, Klebsiella, Pseudomonas spp of *Staph aureus* if hospital acquired 2 marks for any 2]

18. (2) [1 mark]

18.(v) Cloxacillin , Amoxicillin /clavulanic acid or Ciprofloxacin [1 mark optional for bonus point]

19. (3) [1 mark]
19(v) Aminoglycosides (Gentamicin or Amikacin) [1 mark : optional for bonus point]

Total marks = 23 [Score = (Marks scored/23)(100)]

Theoretical basis of making antibiotic choices in Question 18 and 19

The question presented dilemmas of antibiotic selection in two clinical scenarios:
A doctor attending a patient is made aware of the following Gram's staining and morphological properties of pathogens implicated in nosocomial surgical wound infection.

a. Gram-positive cocci (Question 18)
b. Gram-negative bacilli (Question 19)

Ampicillin, Co-trimoxazole and Cefotaxime only are available. The prescribing doctor is required to select one out of these three antibiotics in treating the infections given above.

Essence of the question: The question was meant to test prescribers' knowledge in

i. most likely of gram-positive cocci and gram negative bacilli to be implicated as pathogens in nosocomial wound infection
ii. activities of patterns of antibiotics provided against said most likely implicating pathogens
iii, most obvious issues, like cost of antibiotic, to be considered in principle as one preferentially selects one antibiotic over others in treating an infection.

In absence of antibiograms that exhibit local pathogen antibiotic sensitivity patterns to formulary antibiotics in Lesotho prescribers were expected to use their knowledge of the sensitivity patterns of target pathogens against indicated antibiotics as known from literature in answering this knowledge test question. The decision on which of the three antibiotics was to be selected among the three given antibiotics on the basis of their activities against target pathogens was based on information derived from antibiograms provided by Guglielmo 1988:725,726 (information same as provided in Guglielmo 2008:56-9,56-10 (Appendix 16 below)

Issues considered in selecting one of the three given antibiotics in treating the specified infections as indicated in questions were as presented below:

a. Gram-positive cocci infections:

S. aureus and *S epidermidis* among gram-positive cocci are the most likely to be implicated in open surgical wounds because of their recognition as normal skin flora and their implications in skin infection and should be targeted in empirical treatment of this kind. Other gram-positive cocci may not be ruled out. What is the degree of susceptibility of this class of pathogens to the three antibiotics is as stipulated in literature and also the costs of the antibiotics are points to consider in selecting one antibiotic over the other two as asked in QUESTION 18..

Unless culture sensitivity test results showed otherwise, all three antibiotics in questions have proven efficacy against streptococci. Ampicillin additionally is effective against Enterococci while Cefotaxime has no activity against this organism (Appendix 16). Co-trimoxazole shows only slight activity against Enterococci. Ampicillin on the other hand showed only slight activity against *S. aureus* and *S. epidermidis* and with no activity against the methicillin resistant forms of these two organisms. Cefotaxime has no activity against methicillin resistant strains of *S. aureus* and *S epidermidis* and enterococci. It also has lesser activity against non methicillin strains of *S. aureus* and *S. epidermidis* compared with Co-trimoxazole which shows remarkable activity against both methicillin resistant and non-methicillin resistant forms of *S. aureus* and *S. epidermidis.* On the basis of cost Co-trimoxazole is far cheaper than Cefotaxime. **Based on both literature reported sensitivity patterns and costs of all three antibiotics CO-TRIMOXAZOLE will be the antibiotic of choice among the three available antibiotics in question 18.**

b. Gram-negative bacilli infection:

Gram-negative aerobes that could be implicated in surgical wounds would most likely include *E. coli, Proteus* spp, *Pseudomonas* spp, *and Klebsiella* spp. Their literature indicated susceptibilities to the listed antibiotics as in the case of gram-positive bacteria should be points to consider in making selection of a preferred antibiotic among the three listed in the question in Question 19

Ampicillin by literature report demonstrates only very slight activity against *E. coli* and *Proteus mirabilis*. It has no remarkable activity against *Klebsiella* and *Pseudomonas*. Both Cefotaxime and Co-trimoxazole on the other hand demonstrate quite remarkable activities against Gram negative bacteria with Cefotaxime having a slight advantage over Co-trimoxazole in this respect by having slight sensitivity against *Pseudomonas aeruginosa*. Co-trimoxazole has no activity against this organism. **Cefotaxime may be selected as an antibiotic of choice over Co-trimoxazole and among three antibiotics in question 19 on the basis of the former's slight activity against Pseudomonas. On the basis of cost Co-trimoxazole may be selected over Cefotaxime.**

Appendix 16

Antibiogram of pathogen susceptibilities to antibiotics (Adapted from Guglielmo 2008: 56-9,56-10)

In Vitro Antimicrobial susceptibility: Aerobic Gram-Positive Cocci

Drugs	*Staphylococcus aureus*	*Staphylococcus aureus (MR)*	*Staphylococcus epidermidis*	*Staphylococcus epidermidis (MR)*	*Streptococci*[a]	*Enterococci*[b]	*Pneumococci*
Ampicillin	+		+		++++	++	+++
Augmentin	++++	+	++++		++++	++	++++
Aztreonam							
Cefazolin	++++		++++		++++		++
Cefepime	++++		++++		++++		+++
Cefoxitin/Cefotetan	++		++		++		+
Cefuroxime	++++		++++		++++		+++
Ciprofloxacin[c]	+++	++	+++	++	+	+	++
Clindamycin	++++	+	++++	+	+++		+++
Cotrimoxazole	++++	+++	++	+	++	+	+
Daptomycin[f]	++++	++++	++++	++++	++++	++++	++++
Erythromycin (azithromycin/ clarithromycin)	++		+		+++		++
Imipenem	++++		++++		++++	++	+++
Levofloxacin (gemifloxacin, moxifloxacin)	++++	++	+++	++	+++	++	++++
Linezolid[f]	++++	++++	++++	++++	++++	++++	++++
Nafcillin	++++		++++		++++		++
Penicillin	+		+		++++	++	+++
Quinupristin/ dalfopristin[d,f]	++++	++++	++++	++++	++++	++++	++++
TGC[e]	+++		++		++++		+++
Tigecycline	++++	++++	++++	++++	++++	++++	++++
Timentin	++++		++++		++++	+	+
Unasyn	++++		++++		++++	++	+++
Vancomycin	++++	++++	++++	++++	++++	+++	++++
Zosyn	++++		++++		++++	++	+++

In Vitro Antimicrobial Susceptibility: Gram-Negative Aerobes

Drugs	*Escherichia coli*	*Klebsiella pneumoniae*	*Enterobacter cloacae*	*Proteus mirabilis*	*Serratia marcescens*	*Pseudomonas aeruginosa*	*Haemophilus influenzae*
Ampicillin	++			+++			++++
Augmentin	+++	++		++++			++++
Aztreonam	++++	++++	+	++++	++++	++++	++++
Cefazolin	+++	+++		++++			+
Cefepime	++++	++++	+++	++++	++++	++++	++++
Ceftazidime	++++	++++	+	++++	++++	++++	++++
Cefuroxime	+++	+++		++++	+		++++
Cotrimoxazole	++	+++	+++	++++	+++		++++
Ertepenem	++++	++++	++++	++++	++++	+	++++
Gentamicin	++++	++++	++++	++++	++++	+++	++
Imipenem/ Meropenem/ Doripenem	++++	++++	++++	+++	++++	++++	++++
Quinolones	+++	++++	+++	++++	++++	++	++++
TGC	++++	++++	+	++++	++++	+	++++
Tigecycline	++++	++++	++++	++	++++	−	++++
Timentin	+++	++	+	++++	+++	+++	++++
Tobramycin	++++	++++	++++	++++	+++	++++	++
Unasyn	+++	+++		++++	++		++++
Zosyn	++++	++++	++	++++	++++	++++	++++

TGC, cefataxime, ceftizoxime, ceftriaxone.

Appendix 17

Letter accompanying questionnaires

M. Adorka (Researcher)
Department of Pharmacy,
National University of Lesotho
P. O. Office Roma 180
Roma, Lesotho

In collaboration with

Dept of Pharmacy Practice
School of Pharmacy
North West University
Potchefstroom Campus
South Africa

Dear Doctor/Nurse Clinician

Attached please find a questionnaire that we would like to solicit your kind assistance in completing for our research team that currently is investigating the use of antibiotics in public health institutions in Lesotho.

Questions embodied in the questionnaire are designed for the purpose of identifying factors and highlighting problems that may need redress should it be desired to outline methods of antibiotic prescription writing for improved treatment outcomes in the management of infections. They are not in any way meant to test your knowledge or ability to rationally prescribe antibiotics as an individual authorised prescriber. As indicated above, this is part of a data collecting process in ongoing study aimed at investigating the use of antibiotics in public health institutions in Lesotho with particular reference to the degree of positive treatment outcomes achieved in the management of infectious diseases in the country's hospitals *vis a vis* the general pattern of antibiotic prescription writing and use in the country. While the study largely is of academic interest, it has the ulterior motive of providing the Ministry of Health vital information it may need in strategizing its health delivery efforts in combating infections for which treatment protocols are yet to be developed in this country. We kindly implore you **to provide frank answers to these questions to the best of your ability and without reference to any text.** By so doing you really would be contributing to the success of this study.

We want to note here for your assurance that any information you provide will be treated as confidential and that they will not be linked to you in anyway. For this purpose, we would neither like you to write your name on this questionnaire nor have it hand delivered to the researcher. We would instead like you to envelop the questionnaires using the researcher self addressed and stamped envelop provided and have it returned by post. Alternatively, you may leave the enveloped questionnaire in the office of the superintendent for collection by a person who will have no way of linking you to the envelop or its contents. Your identity will by this means not be known to the researcher and his team. Our appreciation of your answering all questions embodied in this questionnaire notwithstanding, we would like to additionally state here that you reserve the absolute right not to respond to any question you don't feel comfortable answering.

We thank you immensely for your involvement and great contribution to this research.

Yours truly,

M. Adorka

Appendix 18
Permission to conduct research - Ministry of Health

MINISTRY OF HEALTH AN
SOCIAL WELFARE
P.O. BOX 514
MASERU

LESOTHO

May 4, 2005 H\PROJ/40

MR. M. ADORKA
FACULTY OF HEALTH SCIENCES
NATIONAL UNIVERSITY OF LESOTHO

Dear Mr. Adorka,

RE: REQUEST FOR PERMISSION TO CONDUCT A RESEARCH IN ANTIBIOTIC PRESCRIBING PATTERN AND USAGE IN PUBLIC HEALTH INSTITUTIONS IN LESOTHO

Thank you for your request on the above subject. I am happy to inform you that the Ministry of Health and Social Welfare gives you permission to conduct your research project in Public Health Institutions in Lesotho including CHAL Hospitals namely: Scotts Hospital and Maluti Hospital however you are advised that the raw data is the property of Ministry of Health & Social Welfare.

Please provide an update regularly to Executive Secretary CHAL, Med.Supt QEII, Motebang Hospital, Berea Hospital and Mafeteng Hospital and a final report of findings to the Ministry. Good Luck.

Sincerely,

DR. C.T. MOOROSI
DIRECTOR GENERAL OF HEALTH SERVICES

CC: CHAL, MED SUPT QEII MOTEBANG HOSPITAL, BEREA HOSPITAL & MAFETENG HOSPITAL

Appendix 19

Permission to conduct research – Maluti Hospital

Maluti Adventist Hospital
(SEVENTH-DAY ADVENTIST CHURCH)
POSTAL ADDRESS: Private Bag X019, Ficksburg. OFS 9730
P.O. Box 11, Mapoteng, Lesotho
Tel (09266) 22540203 • Fax (09266) 22540230

12-5-05

Dear Mrs Adorka,

We do agree in principle that you can conduct research at Maluti Hospital, with the condition that we are not able to do any extra work above our usual practice.

Sincerely

Dr W. HURLOW

Appendix 20

Permission to conduct research - Scott Hospital

Comprehensive Health Care
Phone: 22360237/52500064/5/6/7
Fax: 22360237/22360001
E-mail: scotthospital@ilesotho.com

SCOTT HOSPITAL

of the

Lesotho Evangelical Church

Private Bag
Morija, 190
Lesotho

27 May 2005

Mr M. Adorka
Faculty of Health Sciences
National University of Lesotho
Roma

Dear Mr Adorka,

REQUEST FOR PERMISSION TO CONDUCT A RESEARCH IN ANTIBIOTIC PRESCRIBING PATTERN AND USAGE IN PUBLIC HEALTH INSTITUTIONS IN LESOTHO

I hereby acknowledge receipt of your letter on the above subject. On behalf of Scott Hospital Management Team I am pleased to inform you that you have been granted permission to conduct the research as you requested.

We will appreciate that all ethical issues be respected and complied with during the research and that you will provide us with the final report of findings.

Yours Sincerely

L. Makakole MD
Medical Director