Antibiotic use and resistance patterns in the Namibian private health sector

D D MOHULATSI

13031198

BPharm, MPH

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

Promoter:	Prof M S Lubbe
Co-promoter:	Prof S Y Essack
Assistant Promoter:	Mr C B Serfontein

March 2016

Preface

Antibiotic usage in Namibia

The current thesis was written up in article format as required by the regulations of the North-West University. The findings of the study are therefore presented in chapter 3 as research articles (published articles, manuscripts submitted for publication or in the process of submission). Four manuscripts have been prepared and submitted for publishing in the following journals:

- *Journal of infectious diseases in developing countries*
- *Iranian journal of public health*
- *Southern African journal of infectious diseases*
- *South African family practice*

Manuscript	Journal	Status
Surveillance of antibiotic use in the private sector of Namibia using medicines claims and sales data	Journal of infectious diseases in developing countries	Accepted for publication (Refer to Annexure G)
Antibiotic use and resistance in the private sector of Namibia	Iranian journal of public health	Submitted for review (Refer to Annexure G)
Public knowledge, attitudes and behaviour towards antibiotic usage in Windhoek, Namibia	Southern African journal of infectious diseases	Accepted for publication. Scheduled for publishing Dec 2015. (Refer to Annexure G)
Antibiotic use in Namibia: prescriber practices for common community infections	South African family practice	Published South African family practice, 2015; 1 (1): 1 -5 DOI: 10.1080/20786190.2015.1024021

The references for the individual manuscripts are cited according to the instructions for authors as required by the different journals. However, a complete reference list is included at the end of the thesis, according to the reference style of the North-West University.

The layout of the thesis is as follows:

- Chapter 1 gives the background and problem statement; and detailed research methodology employed in carrying out the study.
- Chapter 2 is a literature review that provides in depth discussion on concepts of antibiotics and resistance, impact of resistance globally and in Namibia, overview of the Namibia health system and regulatory management of antibiotics in Namibia.
- Chapter 3 provides the findings (results) of the study in article format. Four articles are presented in the style of the journals published or submitted to.
- Chapter 4 integrates the different phases and manuscripts of the study in the conclusions, recommendations and limitations.

The annexures and references will follow at the end.

Acknowledgements

- He who is mighty has done great things for me. Holy is His name (Luke 1: 49). May the Lord of Hosts forever be magnified!

- To Prof Lubbe and Essack, thank you for your leadership, guidance, patience and encouragement from the beginning until the end.

- To my darling husband, Bonnie Pereko and my wonderful children, Lethabo and Reabetswekhumo, your love, support, understanding and sacrifice have made it all possible. Thank you from the bottom of my heart. I love you dearly.

- To my mother Mrs Titilayo Goroh, my brother Mr Joseph Rushubiza, my sister Edla Kaumbi, my dear friend Dr Lawrence Kahindi, thank you so much for your encouraging words, your prayers, steering me on and helping out in anyway.

- I also wish to specially appreciate the medical aid fund, the wholesaler, pharmacists, doctors and members of the community who participated in the study. A special word of gratitude goes to Dr Braan van Greunen and Mr Advance Manghonzo.

Abstract

Antibiotic use and resistance patterns in the Namibian private health sector

The general aim of this study was to understand antibiotic use in the private health sector of Namibia. Specifically, the study set out to ascertain the relationship, if any, between prescribing patterns, antibiotic use and antibiotic susceptibility patterns.

The study employed a mixed method approach, using a mixture of surveys and available data from databases to examine the association between antibiotic use and local resistance, prescribing practices, consumer behaviour as well as knowledge of antibiotics. A retrospective analysis of antibiotic wholesale data and prescription claims data from a medical insurance fund administrator for the period 2008 to 2011 were used to quantify trends in antibiotic use. Laboratory annual antibiogram reports for 2005 to 2011 were used for sensitivity data. Cross-sectional surveys based on self-administered questionnaires were used to determine prescriber practices and patient knowledge and behaviour regarding antibiotics use. Six hundred questionnaires were distributed to patients through community pharmacies in Windhoek and the data were collected between 1 March 2013 and 30 June 2013. The doctors' survey employed a web-based questionnaire which was distributed through professional associations. This data were collected from 1 March 2014 to 31 July 2014.

The study uncovered high antibiotic usage (26.8 DDD/1000/day) in the private sector of Namibia with increasing trends in usage over the study period. An overall 25% increase in antibiotic usage was observed over the four-year period. Antibiotic usage was the highest among females (53%) and in the age group 18 to 45 years (41%). It was also the highest in Windhoek, the capital (34%). Overall, wholesale data showed higher antibiotic use than prescription claims data obtained from the medical insurance fund administrator. However, both sources showed similar patterns of antibiotic use. Penicillins were the highest used pharmacological group, followed by cephalosporins and macrolides. The most commonly used active ingredients were amoxicillin with clavulanic acid (8.25 DID prescription claims; 8.32 DID wholesale); cefuroxime (5.94

DID prescription claims; 6.23 DID wholesale) and clarithromycin (3.2 DID) for prescription claims data and doxycycline (4.05 DID) for wholesale data. The study further found a preference for broad spectrum and newer antibiotics.

Consumption patterns observed in the private sector of Namibia are not unique and compare with those in various European countries as well as other developed and developing countries. Prescriptions claims data were found to be a more reliable data source for the quantification of antibiotic use because calculations have been validated by the medical insurance fund administrator and are also close to actual consumption data, that is, actual quantities dispensed to the patient.

Resistance trends showed very slight changes over the years. The greatest resistance was observed with chloramphenicol (18%). E. coli and S. aureus showed great resistance to amoxicillin (23% and 7%, respectively). Older antibiotics showed greater resistance patterns compared to newer antibiotics. A year-on-year comparison of resistance and use showed no correlation. However, increases in statistical significance were observed when correlating use in earlier years with sensitivity of later years showing that resistance is a function of use and time. Correlating earlier antibiotic use with later resistance also showed that, as the volume of antibiotic consumption increases, the time to reach the same strength of correlation is shorter. This shows that an increase in the volume of antibiotic consumption increases the selection pressure for the development of resistance.

As with consumption patterns, resistance patterns observed in this study are not peculiar to the Namibian private sector, but are similar to those reported elsewhere in Africa, including South Africa.

The study revealed that both awareness of local antimicrobial sensitivity rates and ownership of national standard treatment guidelines among prescribers were poor (20% and 31%, respectively). The common practice among prescribers was to treat community-acquired infections empirically. The reported first-line antibiotics of choice were the combination of amoxicillin with clavulanic acid for upper respiratory tract

infections and ciprofloxacin for urinary tract infections. Antibiotic prescribing was not in line with national standard treatment guidelines and for most common outpatient infections, prescribing were also not in line with local sensitivity patterns.

Assessing public knowledge and behaviour confirmed that antibiotic usage is high in the private sector and that antibiotics are used mainly for respiratory tract infections (specifically colds and flu symptoms). The study further revealed a prevalence of 15% of self-medication with antibiotics mainly obtained from pharmacies without a prescription.

On a positive note, the study uncovered that only 14% of the public reported that they request antibiotics and 80% reported that they complete their antibiotic course. Gaps in the public's understanding of antibiotics were observed. Sixty-four percent (64%) of the public respondents thought that antibiotics were effective against viruses with just less than half admitting that they should take an antibiotic for a cold. On the other hand, 72% of respondents understood that the unnecessary use of antibiotics makes them ineffective.

In order to improve prudent use of antibiotics in Namibia, it is important to regularly monitor antibiotic use and resistance patterns in both the public and private sector. Measures to discourage the over-the-counter sale of antibiotics, promote rational prescribing, encourage adherence to national standard treatment guidelines, increase awareness of local sensitivity patterns and educate patients on antibiotics and their use should be explored and implemented.

Key words: antibiotic use, Namibia, prescribing patterns, resistance patterns, consumer behaviour

Opsomming

Antibiotikagebruik en weerstandbiedenheidspatrone in die Namibiese private gesondheidsektor

Die algemene doelwit van hierdie studie was om antibiotikagebruik in die private gesondheidsektor van Namibië te verstaan. Die studie het spesifiek gepoog om die verband, indien enige, tussen voorskryfpatrone, antibiotikagebruik en antibiotika weerstandbiedenheidspatrone te bepaal.

Die studie het van 'n gemengde metodebenadering gebruik gemaak, deur van opnames en beskikbare databasisse gebruik te maak om die verband tussen antibiotikagebruik en plaaslike weerstand, voorskryfpatrone, verbruikersgedrag sowel as kennis van antibiotika te ondersoek. 'n Retrospektiewe ontleding van antibiotika groothandel- en voorskrifeisdata van 'n mediese versekeringsfonds-administrateur vir die tydperk 2008 tot 2011 is gebruik om tendense in antibiotikagebruik te kwantifiseer. Jaarlikse laboratorium antibiogramverslae vanaf 2005 tot 2011 is as sensitiwiteitsdata gebruik. Deursnee-opnames, gebaseer op self-geadministreerde vraelyste, is gebruik om voorskryfpraktyke en pasiëntkennis en -gedrag ten opsigte van antibiotikagebruik te bepaal. Seshonderd vraelyste is versprei aan pasiënte regoor gemeenskapsapteke in Windhoek. Data is vanaf 1 Maart 2013 tot 30 Junie 2013 ingesamel. Die geneeshere se opname het gebruik gemaak van 'n webgebaseerde vraelys wat versprei is deur middel van professionele verenigings. Hierdie data is vanaf 1 Maart 2014 tot 31 Julie 2014 ingesamel.

Die studie dui op hoë antibiotikagebruik (26.8 DDD/1000/dag) in die private sektor van Namibië, met toenemende tendense in die vier jaar periode. Daar was 'n algehele 25% toename in antibiotikagebruik gedurende die vierjaartydperk wat ondersoek is. Antibiotikagebruik was die hoogste tussen vroue (53%) en in die 18 tot 45 jaar-ouderdomsgroep. Dit was ook die hoogste in Windhoek, die hoofstad (34%). Oor die algemeen het groothandeldata hoër antibiotikagebruik getoon as voorskrifeisdata wat vanaf die mediese versekeringsfonds-administrateur ontvang is. Beide bronne het

egter soortgelyke antibiotikagebruikspatrone getoon. Penisillien was die mees gebruikte farmakologiese groep, gevolg deur kefalosporiene en makroliede. Die mees algemeen gebruikte aktiewe bestanddele was amoksisillien met klavulaansuur (8.25 DID-voorskrifeise; 8.32 DID-groothandel); kefuroksiem (5.94 DID-voorskrifeise; 6.23 DID-groothandel) en klaritromisien (3.2 DID) vir voorskrifeisdata en doksisiklien (4.05 DID) vir groothandeldata. Die studie het verder ook 'n voorkeur gevind vir breë spektrum- en nuwer antibiotika.

Verbruikspatrone wat waargeneem is in die private sektor van Namibië is nie uniek nie en vergelyk goed met dié in verskeie Europese lande sowel as ander ontwikkelde en ontwikkelende lande. Voorskrifeisdata is as meer betroubare databron vir die kwantifisering van antibiotika gebruik gevind, aangesien berekeninge gevalideer is deur die mediese versekeringsadministrateur en is na aan werklike verbruiksdata, dit is, werklike hoeveelhede wat aan die pasiënt verskaf is.

Weerstandstendense het baie klein veranderinge oor die jare getoon. Die grootste weerstand is waargeneem met chlooramfenikol (18%). E. coli en S. aureus het hoë weerstand getoon vir amoksisillien (23% en 7%, onderskeidelik). Ouer antibiotika het hoër weerstandspatrone getoon in vergelyking met nuwer antibiotika. 'n Jaar-tot-jaar-vergelyking van weerstand en gebruik het geen korrelasie getoon nie. Toenames in statistiese beduidendheid is egter waargeneem met vergelyking van verbruik in vroeër jare met sensitiwiteit van latere jare wat toon dat weerstand 'n funksie van verbruik en tyd is. Wanneer vroeër antibiotikagebruik met latere weerstand gekorreleer word, is getoon dat soos die volume van antibiotikaverbruik toeneem, is die tyd om dieselfde sterkte van korrelasie te bereik, korter. Dit toon dat 'n toename in die volume van antibiotikagebruik, verhoog die druk vir die ontwikkeling van weerstand.

Soos met verbruikspatrone, is weerstandspatrone waargeneem in hierdie studie nie uniek tot die Namibiese private gesondheidsektor nie, maar is soortgelyk aan tendense wat elders in Afrika en Suid-Afrika gerapporteer is.

Die studie het onthul dat beide bewustheid van plaaslike antimikrobiese sensitiwiteitskoerse en eienaarskap van nasionale standaardbehandelingsriglyne tussen voorskrywers swak is (20% en 31%, onderskeidelik). Die algemene praktyk tussen voorskrywers was om gemeenskapsverkrygde infeksies empiries te behandel. Die gerapporteerde eerste-lyn-antibiotika van keuse was die kombinasie van amoksisillien met klavulaansuur vir boonste lugweginfeksies en siprofloksasien vir urienweginfeksies. Die voorskryf van antibiotika was nie in lyn met nasionale standaardbehandelingsriglyne nie, en vir meeste algemene buitepasiënt-infeksies was voorskrifte ook nie in lyn met plaaslike sensitiwiteitspatrone nie.

Die assessering van publieke kennis en gedrag het bevestig dat antibiotikagebruik in die private sektor hoog is en dat antibiotika hoofsaaklik vir lugweginfeksies gebruik word (spesifiek verkoue- en griepsimptome). Die studie het verder ’n 15%-voorkoms van selfmedikasie met antibiotika gevind, wat hoofsaaklik vanaf apteke sonder ’n voorskrif bekom is.

Aan die positiewe kant het die studie onthul dat slegs 14% van die publiek antibiotika versoek en dat 80% noem dat hulle die kursusse voltooi. Gapings in die publiek se begrip van antibiotika is verder waargeneem. Vier-en-sestig persent van die publieke respondente het gedink dat antibiotika effektief teen virusse is, en net minder as die helfte het erken dat antibiotika vir ’n verkoue geneem moet word. Aan die ander kant het 72% van publieke respondente verstaan dat die onnodig gebruik van antibiotika dit oneffektief maak.

Om antibiotikagebruik in Namibië te verbeter is dit belangrik om antibiotikagebruik en weerstandbiedenheidspatrone in beide die openbare en private sektore gereeld te monitor. Maatstawwe om die oor-die-toonbank-verkoop van antibiotika te beperk, om rasionele voorskrifpatrone te bevorder, om navolging van nasionale standaardbehandelingsriglyne aan te moedig, om bewustheid van plaaslike sensitiwiteitsriglyne te verbeter, en om pasiënte in te lig oor antibiotika en sy gebruik, is aspekte wat ondersoek en geïmplementeer moet word.

Sleutelwoorde: antibiotikagebruik, Namibië, voorskryfpatrone, weerstandbiedenheidspatrone, verbruikersgedrag

Author contributions

The manuscripts were co-authored by the study promoters (the promoter and co-promoter). The co-promoter for the study was Prof Sabiha Yussuf Essack, a recognised authority in the field of antibiotics. Both the promoter and co-promoter gave consent that the articles be used as part of this thesis. The specific contributions of each author are stipulated below.

Article 3.1: *Surveillance of antibiotic use in the private sector of Namibia using medicines claims and sales data*.

Author	Contribution
DD Pereko	Conception and design of the study (design of data collection tools, design of data extraction tools) Acquisition of data Analysis of data Interpretation of data Writing of the first drafts of the manuscript
MS Lubbe	Guidance and supervision in the conceptualization and design of study Overseeing the design of data collection and data extraction tools Substantial contribution in the analysis of data Guidance on the interpretation of data Guidance and critical revision of the manuscripts
SY Essack	Guidance and supervision in the conceptualization and design of study Overseeing the design of data collection and data extraction tools Substantial contribution in the analysis of data Guidance on the interpretation of data Guidance and critical revision of the manuscripts

Article 3.2 *Antibiotic use and resistance in the private sector of Namibia*

Author	Contribution
DD Pereko	Conception and design of study (design of data collection tools, design of data extraction tools, field testing of data and data collection) Acquisition of data Analysis of data Interpretation of data Writing of manuscripts
MS Lubbe	Guidance and Supervision in the conceptualization and design of study Guidance on the interpretation of data Guide and critical revision of the manuscripts
SY Essack	Guidance and Supervision in the conceptualization and design of study Provide guidance through the data extraction and collection process Substantial guidance in the analysis of data Guidance on and critically review of the interpretation of data Guide and critical revision of the manuscripts

Article 3.3: *Public knowledge, attitudes and behaviour towards antibiotic usage in Windhoek, Namibia*

Author	Contribution
DD Pereko	Conception and design of study data (design of data collection tools, design of data extraction tools, field testing of data and data collection) Acquisition of Analysis of data

	Interpretation of data Writing of first draft of the manuscripts
SM Lubbe	Guidance and supervision in the conceptualization and design of study Overseeing the design of data collection and data extraction tools Substantial contribution in the analysis of data Guidance on the interpretation of data Guidance and critical revision of the manuscripts
SY Essack	Guidance and supervision in the conceptualization and design of study Overseeing the design of data collection and data extraction tools Substantial contribution in the analysis of data Guidance on the interpretation of data Guidance and critical revision of the manuscripts

Article 3.4: *Antibiotic use in Namibia: prescriber practices for common community infections*

Author	**Contribution**
DD Pereko	Conception and design of study (design of data collection tools, design of data extraction tools, field testing of data and data collection) Acquisition of data Analysis of data Interpretation of data Writing of manuscript
SM Lubbe	Guidance and Supervision in the conceptualization and design of study Overseeing the design of data collection and data extraction tools Substantial contribution in the analysis of data

	Guidance on the interpretation of data Guidance and critical revision of the manuscripts
SY Essack	Guidance and Supervision in the conceptualization and design of study Overseeing the design of data collection and data extraction tools Substantial contribution in the analysis of data Guidance on the interpretation of data Guidance and critical revision of the manuscripts

The following statement provided by the co-authors confirms their individual roles in the manuscripts and give their permission that the manuscript may form part of this thesis.

I declare that I have approved above-mentioned manuscripts and that my role in these manuscripts, as indicated above, is representative of my actual contributions and I hereby give my consent that it may be published as part of the PhD study of D D Pereko.

Prof M S Lubbe

Prof S Y Essack

Table of contents

List of Tables

List of Figures

Abbreviations

ACT	Artemisinin containing therapies
ADR	Adverse Drug Reactions
AIDS	Acquired immunodeficiency syndrome
AMR	Antimicrobial Resistance
APIC	Professionals in Infection Control and Epidemiology
APUA	Alliance for Prudent Use of Antibiotics
ATC	Anatomical Therapeutic Classifications
BRICS	Brazil, Russia, India, China and South Africa
CA-MRSA	Community Acquired - Methicillin Resistant *Staphylococcus Aureus*
CAP	Community Acquired Pneumonia
CDC	Centres for Disease Control and Prevention
CPD	Continuing Professional Development
DDD	Defined Daily Dosage
DID	DDD/1000 population/day
DNA	Deoxyribonucleic acid
ESAC	European Surveillance of Antimicrobial Consumption
FDA	Food and Drug Administration

GDP	Gross Domestic Product
HA-MRSA	Hospital Acquired - Methicillin Resistant *Staphylococcus Aureus*
HIV	Human Immunodeficiency Virus
HIVDR	HIV drug resistance
IDSA	Infectious Disease Society of America
INRUD	International Network for Rational Use of Drugs
MDR-TB	Multi-drug resistant tuberculosis
MIMS	Monthly Index of Medical Specialities
MoHSS	Ministry of Health and Social Services
MRSA	Methicillin Resistant *Staphylococcus Aureus*
NAAR	Namibians against Antimicrobial Resistance
NAMAF	Namibia Association of Medical Aid Funds
NAPPI	National Pharmaceutical Product Index
NEMLIST	Namibia Essential Medicines Lists
NIAID	National Institute of Allergy and Infectious Diseases
NIP	Namibia Institute of Pathology
NMP	National Medicines Policy
NMRC	Namibia Medicines Regulatory Council
NWU	North-West University
PHC	Primary Health Care

PhV	Pharmacovigilance
PMIS	Pharmacy Management Information System
PSN	Pharmaceutical Society of Namibia
QSL	Quality and Surveillance Laboratory
TB	Tuberculosis
THE	Total Health Expenditure
TIPC	Therapeutic Information and Pharmacovigilance Centre
SAS	Statistical Analytical System
SHOPS	Strengthening Health Outcomes through the Private Sector
SPSS	Statistical Package for the Social Sciences
STG	Standard Treatment Guideline
STI	Sexually Transmitted Infection
TIPC	Therapeutic Information and Pharmacovigilance Center
UTI	Urinary Tract Infection
VEN	Vital, Essential or Necessary
WHA	World Health Assembly
WHO	World Health Organization
XDR-TB	Extremely Drug Resistant TB

Definition of terms

Antibiotics - naturally occurring or synthetic low molecular weight substances that selectively inhibit the growth or multiplication of bacteria or kill bacteria cells directly.

Antibiotic resistance – the ability of microbes to grow in the presence of antibiotics thus rendering antibiotic ineffective

Antimicrobial sensitivity testing – a test carried out to determine which antibiotic is effective against a specific bacteria

Private health sector – healthcare providers and health facilities that are outside of the public health system

Public health sector – healthcare that is provided for and funded for by the government

Surveillance – systematic collection, analysis and dissemination of antibiotic-related data (i.e. how antibiotics are being used, how much is being used and monitoring resistance patterns of pathogens)

Chapter 1: Introduction

This chapter introduces the study with an overview on antibiotic use and antimicrobial resistance globally and in the region. The chapter also discusses the problem statement, significance of the study, research objectives, and research methodology, followed by a discussion of the chapter division.

1.1. Background

Since antibiotics were first used clinically during the 1940s, they have become one of the pillars of modern medicine (Cars *et al.*, 2011:68; Rice, 2008:1079; Spellberg *et al.*, 2008:162; Pendleton *et al.*, 2013:297) resulting in many health gains including a decrease in morbidity and mortality due to infectious disease (Alanis, 2005:697; Chandy *et al.*, 2013:229; Finley *et al.*, 2013:1; Holloway *et al.*, 2011:152; Rice, 2008:1079). Hailed as miracle drugs and panacea of medicine, their use became widespread (Alanis, 2005:698; Beovic, 2006:280; Mollahaliloglu *et al.,* 2012:281; WHO, 2014a:1) to such an extent that the Centres for Disease Control and Prevention (CDC) described antibiotics as being among the most commonly used drugs for human use (CDC, 2013:11), thoughts previously echoed by Buke *et al.* (2003:63).

This notion of widespread antibiotic use has further been supported by several studies that have demonstrated increases in antibiotic consumption with time. For instance, in Europe, outpatient antibiotic use increased continuously from 1997 to 2003 in eight of 25 studied countries (Ferech *et al.*, 2006:404).This was particularly pronounced for certain classes of antibiotics. Macrolides, lincosamides and streptogramin consumption increased in 14 countries, particularly the intermediate and long-acting macrolide analogues (Coenen *et al.*, 2006b:421-422), and second- and third-generation cephalosporins in 12 countries (Coenen *et al.*, 2006a). These findings are similar to those reported by Stille *et al.* (2004:1209) in their study to assess trends in second generation macrolide use among children in the United States. In Italy, Vaccheri *et al.,* (2008:956) also reported an increase in antibiotic use in hospitals over a three-year period. More recently, a study conducted by Huang *et al.* (2011:2644) in Norway

showed a marked increase in antibiotic use, while another study conducted in The Netherlands showed a significant increase in antibiotic use from 52.3% in 2003 to 69.8% in 2009 (Kwint *et al.*, 2012:2285).

High antibiotic usage is not only an occurrence of developed countries, as the studies stated above might suggest. It has been equally noted in developing countries. A report by the Lancet Infectious Disease Commission (2013:1) revealed that increased use of antibiotics was not a phenomenon only of high income countries but has also been observed across all countries regardless of income status (Lancet Infectious Disease Commission, 2013:1). A recent survey conducted by the Princeton University confirms the Commission's claim by reporting that 76% of all increases in antibiotic use globally could be attributed to the five BRICS countries – Brazil, Russia, India, China and South Africa (Van Boeckel *et al.*, 2014:746). Other authors similarly indicate high antibiotic use in Africa (Desalegn, 2013:3; Kimang'a, 2012:136; Ntšekhe *et al.*, 2011:11; WHO 2011a:6). In 2001, Namibia also reported a 12% increase in antibiotic usage between 1997 and 2001 (Lates & Shiyandja, 2001:10).

Unfortunately, this increased antibiotics use has dampened the euphoria over the conquest of deaths due to bacterial infections as a result of the threat of the development of resistance to antimicrobials (Ashley *et al.*, 2011:1167; CDC, 2013:11; MacGowan, 2008:ii105; WHO, 2012:3).

Antimicrobial resistance is the ability of microbes to grow in the presence of a medicine that would normally kill them or limit their growth (Aziz, 2013:1067; Hashemi *et al.*, 2013:384; NIAID, 2009; WHO, 2014b). Antimicrobial resistance (hereafter referred to as antibiotic resistance) has been reported as an increasing threat to human health (Costelloe *et al.*, 2014:30; Holloway *et al.*, 2011:152; Mulvay & Simor, 2009:408; Nyasulu *et al.*, 2012:8; Wood *et al.*, 2013:237; World Economic Forum, 2013:11).

Experts worry that since antibiotic resistance is increasing (Ashley *et al.*, 2011:1168; Okeke *et al.*, 2007:1640; Simonsen *et al.*, 2004:929; Sirinavin, 2004:94; Spellberg *et al.*, 2008:155) and the number of new antibiotics in development is limited (Bartlett, 2011:S5; Boucher *et al.*, 2009:7; Han & Ramsay, 2013:368; Freire-Moran *et al.,*

2011:122; Pendleton *et al.*, 2013:297) a situation may be approaching where health care professionals will not have appropriate medications to effectively treat all patients who develop infections.

After more than 70 years of widespread use, evolution of disease-causing microbes has resulted in many antimicrobials losing their effectiveness (Byarugaba, 2004:105; CDC, 2010:2; Chandy *et al.*, 2013:229; Freire-Moran *et al.*, 2011:118; IDSA, 2009:1; Kimang'a, 2012:135; Nyasulu *et al.*, 2012:8; Okeke *et al.*, 2007:1640).

While there are many factors that can lead to antibiotic resistance, high exposure to antibiotics is probably the most important cause (CDC, 2013:11; Goossens *et al.*, 2005:571; Vander Stichele *et al.,* 2004:420). The relationship between antibiotic use and resistance has been widely documented (Beovic, 2006:1; Bartlett, 2011:S4; Cars *et al.*, 2011:68; Furgerson 2004:39; Kimang'a, 2012:137; WHO, 2007:web page). In fact, numerous studies have indicated a clear relation between antimicrobial use and resistance. In 2005, Goossens and colleagues (2005: 583) conducted a study in Europe on the association between outpatient antibiotic use and resistance. The study showed that there were higher rates of antibiotic resistance in countries which had higher antibiotic consumption rates, suggesting an association between antibiotic consumption and resistance.

In another study in Europe in 2006, Ferech and colleagues (2006:404) concluded that "geographic differences in the outpatient antibiotic use correlate at ecological level with geographic variation of resistance in Europe". Malhotra-Kumar *et al.* (2007:489) in a study conducted in Belgium found that at individual level there is a direct correlation between macrolide antibiotic exposures and resistance. They further concluded that "*antibiotic use is an important driver of the emergence of antibiotic resistance in vivo. In view of the reported consequences of antibiotic use, prescribers should take into account the striking ecological side-effects of antibiotics when prescribing such drugs to their patients*." While in the previous year, Coenen *et al.* (2006b:422) found that there was higher macrolide resistance in countries that predominantly used intermediate and long acting analogues. Again in 2007, a study conducted in the UK by Hillier and

colleagues found an association between antibiotic use and resistance (Hillier *et al.*, 2007:97). This was in contrast to what they reported in 2002 (Hillier *et al.*, 2002:245).

Similar results of the association between antibiotic use and resistance were reported in Taiwan (Bennett *et al.*, 2009:24), in Denmark (Skjøt-Rasmunsen, 2012:87; Jensen *et al.*, 2010:1289), in India (Wattal *et al.*, 2005:157) and also through systematic reviews conducted in 2009 and 2013 (Costelloe *et al.*, 2010:11; Bell *et al.*, 2014:25). Accordingly, resistance has been shown to be most prevalent in countries in which antibiotic use is particularly high (Bell *et al.*, 2014:27; Bronzwaer *et al.*, 2002:280; Goossens *et al.*, 2005:585).

The above referenced studies refer to Europe and other parts of the world and yet in Africa also, the problems of resistance to antibiotics have been noted. In a study conducted in Northern Ghana, it was noted that enteric bacteria from children are highly resistant to antibiotics used in that area (Djie-Maletz, 2008:1318). Similar trends have been reported in other parts of Africa. In Nigeria, studies have observed temporal trends in the prevalence of resistance among enteric organisms, such as *Escherichia coli* (Okeke *et al.*, 2000:395) and *Shigella* (Iwalokun *et al.*, 2001:188). These studies showed that there was in the last 15 years increasing prevalence in resistance to commonly used antimicrobials, including trimethoprim-sulphamethoxazole, ampicillin, tetracycline and chloramphenicol (Okeke & Sosa, 2008:3). Similar patterns were reported in a study conducted in Mmabatho, South Africa (Kinge *et al.*, 2010:47). Recently in 2012, Kimang'a (2012, 136-137) reported resistance trends in important pathogens similar to what is reported in the developed world, all across Africa. These pathogens include trends of resistance to pathogens such as *Staphylococcus aureus, Neisseria gonorrhoeae, Klebsiella pneumonia, Streptococcus pneumoniae, Escherichia coli, Pseudomonas aeruginosa* and *Shigella spp*. (Kimang'a, 2012:136-137).

In the 3rd National Medicines Use survey conducted among 1 132 patients in Namibia by Lates and Shiyandja (2001:10), the results demonstrated that the use of antibiotics in the public health sector of Namibia increased from 39% in 1997 to 51% in 2001. This study was done only in the public health sector. There is currently no documented

evidence that any antibiotic usage studies were conducted in the private health sector of Namibia.

The occurrence of multi-drug resistant strains of bacteria is associated with treatment failures, higher morbidity and mortality, and increased cost (Goossens, 2000; Alanis, 2005:698), as cheaper and older agents are no longer effective and will therefore have to be replaced with newer more expensive ones. This was pointed by Laxminarayan and Malani (2007) (cited by Management Sciences for Health, 2008:4), when they noted that the annual additional cost of treating hospital-acquired infections from six species of antibiotic-resistant bacteria was estimated to be at least US$1.3 billion in 1992. Okeke *et al.* (2005) (cited by Management Sciences for Health 2008:4) noted that the costs associated with antimicrobial resistance (AMR) among outpatients in the United States have been estimated to lie between US$400 million and US$18.6 billion while in 2014 the Infectious Disease Society of America (IDSA) reported the cost of treating resistant infections to be between US$21 billion and US$34 billion (IDSA). A study conducted by Nicolau (2002:66) showed that the rise in antimicrobial resistance was linked to increased costs of treating patients with community-acquired respiratory tract infections. Apart from increased length of stay in hospital, average pharmacy (antibiotic) costs were much higher in penicillin-resistant patients as compared to penicillin-susceptible patients (US$736 versus US$231). Welte *et al.* (2010) found that community acquired pneumonia was associated with high rates of hospitalisation and length of hospital stay. The review showed that the clinical and economic burden of community acquired pneumonia (CAP) in Europe is high.

The economic burden of antibiotic resistance in developing countries can be illustrated by the development of multi-drug resistant tuberculosis. Pooran and colleagues reported that in South Africa treating drug-resistant TB cost up to 103 times more than treating drug-sensitive TB (Pooran *et al.*, 2013:8). This is similar to what was reported by Management Sciences for Health (2008:4) that the cost of a full course of drug treatment for MDR-TB in the North-West Province of South Africa is R26 354 compared with R215 for drug-susceptible TB. Data from Peru support the hypothesis that MDR-TB is much more expensive to treat than susceptible tuberculosis strains that are resistant

to only one or two medicines-costs for full course of treatment were estimated at US$8 000 for MDR-TB, as opposed to US$267, for susceptible tuberculosis (Okeke *et al.,* 2005:488). Howard (2004:587) also argues that the opportunity cost of resistance-induced substitution for amoxicillin alone with amoxicillin and clavulanic acid is in the order of US$8 per patient. The high cost of treating drug-resistant infections may exceed the financial capacity of many patients and financing mechanisms such as medical aid schemes/funds and governments.

The other cost to bear in mind is the cost of the disruption of the delivery of healthcare services caused by multiple antibiotic-resistant bacteria (cost of isolation, cross-infection control and cancelled procedures) and, as this cost is not easily recognised or accounted for, it is frequently forgotten (Hawkey, 2008:i2). Other costs often forgotten with overuse of antibiotics are increased healthcare costs due to complications arising from toxicity, allergies and drug interactions (Nicolau, 2002:66).

Namibia has a very active private health sector, including private hospitals, doctors, nurses, primary health care clinics, pharmacists and social workers. The registration and sale of medicines in Namibia is legislated under the Medicines and Related Substances Control Act (13 of 2003). Only medicines registered with the Namibia Medicines Regulatory Council can be sold in the country. Also under the Act, antibiotics can only be sold on a valid prescription from a medical doctor or a health care professional licensed to prescribe such antibiotics. Private healthcare is primarily financed through medical or health insurance (O'Hanlon *et al.*, 2010:26).

Namibia's health insurance industry is well developed and organised into open and closed medical insurance schemes. Large and medium-sized companies and the public sector provide access to health insurance for their employees. Therefore, a significant number of Namibians are covered under health insurance plans and use the private sector for health care. According to the Namibia Association of Medical Aid Funds (NAMAF), in 2014 there were 388 371 people covered by medical insurance-this translates to 16% of the total population of Namibia. With private health care providers being accessible, it is expected that there are more patients accessing private health care in Namibia. (NAMAF interview, 2014, unpublished).

In the public health sector of Namibia there are standard treatment guidelines that are used in the management of patients at all levels of care. These guidelines include use of antibiotics in different disease states. However, in the private health sector in Namibia there are no guidelines for the use of antibiotics and it is not known what the antibiotic prescribing practices are.

1.2. Problem statement

Rational use of antibiotics is important as inappropriate use can adversely affect patients (Desalegn, 2013:171; WHO, 2011:1), cause emergence of resistance (Auta *et al.*, 2013:1087; Chandy, 2008:175; Jose *et al.*, 2013:324; Kotwani *et al.*, 2012:311) and increase health care costs (Desalegn, 2013:171; WHO, 2011:1). Antimicrobial resistance makes it harder to eliminate infections from the body. As a result of a microbe's ability to survive in spite of antimicrobials, some infectious diseases are now more difficult to treat than they were just a few decades ago (Lancet Infectious Disease Commission, 2013:1; NIAID, 2011).

The consequences are severe because infections caused by resistant microbes fail to respond to treatment, resulting in prolonged illness and greater risk of death (Freire-Moran *et al.*, 2011:119; Mulvey & Simor, 2009:413; Nyasulu *et al.*, 2011:8; Kim *et al.*, 2011:742; French, 2005:1515; French, 2010:S5).

When infections become resistant to first-line antimicrobials, treatment has to be switched to second- or third-line drugs, which are nearly always much more expensive (Cars *et al.*, 2011:68; Okeke *et al.*, 2007:1640; Cars & Nordberg, 2005:103) and sometimes more toxic as well (Byarugaba, 2004:106; Okeke *et al.*, 2005:481; Levy, 2005:1449; French, 2010:S5). In 2009, Nelson *et al.* (2009:16-17), reported the cost associated with the use of second line treatment for tuberculosis, malaria and HIV/AIDS to be 175, six and 14 times more expensive than first line treatment, respectively. In many countries, the high cost of such replacement drugs is prohibitive, with the result that some diseases can no longer be treated in areas where resistance to first-line drugs is widespread (Ashley *et al.*, 2011:1167; Cars *et al.*, 2011:68). An example of such is Burkina Faso which had to resort to chloroquine (even though resistance to

chloroquine has been proven) for the treatment of malaria due to unavailability of funds to purchase artemisinin-containing therapies (ACT), which are 10 times more expensive, or pyremethamine-sulfadioxide and amodiaquine (Kouyate *et al.*, 2007:999). Furthermore, a study in Ghana (Bosu & Mabey, 1998) found that the recommended treatment for pelvic inflammatory disease, ceftriaxone and ciprofloxacin, were more expensive and not available in hospitals, health centres or private sector. Drugs which were less expensive and more readily available could however not be used because of resistance (Bosu & Mabey, 1998).

In order to minimise the development of resistance, antibiotic use should be routinely monitored and correlated with antibiotic resistance trends by quality-assured surveillance on antibiotic susceptibility and antibiotic use and corrective interventions put in place. However, data on antibiotic use are scarce. This was noted by Goossens *et al.* (2005:579). He further noted that factors that determine difference in use of antibiotics in different countries are not fully understood but can be explained by variations in incidence of community acquired infections and drug regulations, among others.

Hutchinson *et al.* (2004:29) argues that *"until such time as fundamental measurements of consumption are routinely available to researchers, advisors, clinicians and policy-makers, it will continue to be difficult to address this growing problem of antibiotic use and related development of resistance*". It is important to note that while most antimicrobial use occurs in community practice, little data exists describing antimicrobial use in community settings (Ashley *et al.*, 2011:1168; Carrie & Zhanel, 1999:871; Kotwani & Holloway, 2011:1).

Similarly, while antibiotic use studies were carried out in the public health sector of Namibia (Lates, 1999; Lates & Shiyandja, 2001), there is no evidence to suggest that antibiotic use and monitoring is being done in the private health sector. There is also no published documented evidence that suggests that resistance pattern monitoring is occurring in the private health sector.

In his paper on emerging infectious diseases in South Africa, Klugman (1998) points out that there is a difference in antibiotic resistance between the public and private health sectors of South Africa, attributing the differences to differences in use. Antibiotic use is influenced by regulatory environment, characteristics of a country's health system, economic incentives and the interplay of the knowledge, expectations and interactions of prescribers and patients (WHO, 2012:34-35).

In Namibia, just like South Africa, there is a dichotomy between public and private healthcare system which affects antibiotic drug selection and use. Medicine use in the public sector is regulated and restricted through the use of the Namibia Essential Medicines List (Nemlist) and standard treatment guidelines (STG). While these are extended to the private sector, medicine use in the private sector is not monitored and therefore drug selection is unrestricted. This difference can result in differences in use as pointed by Klugman (1998).

In an effort to support the preservation of antibiotics through rational use, it is important to understand how antibiotics are used in the private health sector of Namibia, as no specific action can be developed if antibiotic consumption and usage trends and resistance patterns are not known.

Considering the importance of prudent antibiotic use to minimise the risk of development of resistance and the lack of information on antibiotic usage in ambulatory patients in the private health sector of Namibia, the study was guided by the questions: What are the antibiotic usage and microbial sensitivity patterns among ambulatory patients in the private health sector of Namibia?

In order to explore this primary research question fully, the following secondary questions were addressed:

- What is the extent and pattern of antibiotic use in Namibia?
- What are the sensitivity/resistance patterns to common antibiotics in Namibia and how do current guidelines compare with these data?
- What is the clinical practice in prescribing antibiotics among doctors?

- What are the public's perceptions and knowledge with regards to antibiotics?

1.3. Significance of the study

In determining the significance of the study, the two questions considered are: is there currently a gap in the field and is the study useful? Despite the global public health importance of resistance and the need for monitoring and surveillance, there is currently no literature to support knowledge of antibiotic use and resistance patterns in Namibia's private health sector.

This study provides unique and valuable information concerning antibiotic usage and sensitivity profiles for common bacteria encountered in the private health sector of Namibia, which can be used to design evidence-based interventions aimed at improving antimicrobial stewardship and therefore reduce resistance. It is hoped that this study will be used as baseline in monitoring and surveillance of antibiotic use and resistance in the Namibian private health sector as recommended in the past WHO resolutions 1998 (WHA 51.17:1), 2005 (WHA A58.14:3) and 2007 (WHA A60.28:2) and re-enforced in the WHO 2011 Policy Package to combat antimicrobial resistance (Leung *et al.*, 2011:391) and the Antimicrobial Resistance Global Report on surveillance of 2014 (WHO, 2014a:71).

1.4. Research aim

The general aim of the study was to ascertain the relationship, if any, between prescribing patterns, antibiotic use and antibiotic susceptibility patterns in the private health sector of Namibia.

1.4.1. Specific research objectives

To satisfactorily answer the already mentioned research questions and attain the study aim, a two-dimensional research approach was used. The approach consisted of a literature review and an empirical study.

1.4.2. Specific research objectives for the literature review

According to Taylor of the Health Sciences Writing Centre of the University of Toronto, literature review is "*an account of what has been published on the research topic by accredited scholars and researchers*" (University of Toronto, 2008). It involves finding, reading, critically analysing and forming conclusions about what is written and published in the research topic (Van der Walt & Van Rensburg, 2011:67).

The aim of the literature review was to establish a theoretical framework of the research topic through conducting a critical analytical appraisal of relevant existing knowledge of the area (Botma, 2010:63). In this study, the literature review was to provide context of antibiotic use and resistance globally and in Namibia.

Specifically, the literature review aimed to:

- Conceptualise the mechanism of action, uses and prescribing principles guiding antibiotic prescribing;
- Investigate from the literature the causes, mechanisms and scope and magnitude of antibiotic resistance;
- Discuss global strategies for addressing antimicrobial resistance;
- Provide broad context for Namibia health care system in order to give an understanding of the management of antibiotics usage within the country context.

The literature review was also used to refine the research methodology, data sources and instruments used in the study.

1.4.3. Specific research objectives for the empirical study

The specific research objectives of the empirical study include the following:

- Identifying and/or evaluating data sources for the quantification of antibiotic usage patterns in ambulatory patients in the private health sector of Namibia;
- Ascertaining susceptibility patterns in the private health sector and determining possible relationships between antibiotic usage and resistance;
- Determining from the perceptions of private doctors (general practitioners and specialists) their behaviour and clinical practice in prescribing antibiotics;

- Examining from the perceptions of the public their behaviour regarding antibiotics use in the community of Windhoek

A summary of the study specific objectives and how they are reported follows below in Table 1-1.

Table 1-1: Summary of study objectives and how addressed

Empirical research objectives	**Study phase**	**Article where reported**
Identifying and/or evaluating data sources for the quantification of antibiotic usage patterns in ambulatory patients in the private health sector of Namibia	Phase 1	Surveillance of antibiotic use in the private sector in Namibia using claims and sales data. Journal: *The journal of infection in developing countries* – Manuscript accepted for publication.
Ascertain susceptibility patterns in the private health care setting and determine possible relationship between usage and resistance.	Phase 2	Surveillance of antibiotic resistance in the private sector in Namibia Journal: *Iranian journal of public health* Manuscript submitted
Examining from the perceptions of the public their behaviour regarding antibiotics use in the community of Windhoek.	Phase 3	Public knowledge, attitudes and behaviour towards antibiotic usage in Windhoek, Namibia. Journal: *Southern African journal of infectious disease* Manuscript accepted for publication
Determining from the perceptions of private doctors (general practitioners and specialists) their behaviour and clinical practice in prescribing antibiotics.	Phase 4	Antibiotic use in Namibia: prescriber practices for common community Infections Journal: *South African family practice* Published online 29 May 2015. South African family practice, 2015; 1 (1): 1 -5 DOI: 10.1080/20786190.2015.1024021

1.5. Research methodology

The following section presents the research methodology undertaken in conducting the study and covers both the literature review and the empirical study component. For the literature review portion, it details how the literature review was conducted. For the empirical section, it describes how the study was conducted and includes: research design, study population, data source and methods of data collection, data analysis, issues of reliability and validity as well as ethical considerations.

1.6. Literature review

Computerised searches of online databases such as PubMed, MEDLINE and the North-West University library online search were used to identify studies and articles that address the study area and research questions. The library database was used as the main source of literature to review. In addition, internet search engine Google and Google scholar, websites of organisations who are authorities in the subject matter were also used.

Key words such as antibiotic resistance, antimicrobial resistance, sub-Saharan Africa, antibiotic usage, resistance patterns, were used in searches to obtain abstracts and those abstracts that were deemed relevant to the study were selected and full articles of these sourced. Bibliographies of most of the sourced articles were also examined to identify other related articles that could have been missed through search engines. Lead authors in the field were also identified and author searches were conducted to see if any of their work was relevant to the study topic.

The Ministry of Health and Social Services Namibia website was used to access policy documents and reports to enable the researchers to define the Namibian healthcare system. Where information deemed critical to understanding the context was not available in published literature, stakeholder interviews were conducted. This was specifically the case for understanding antibiotic management in the Namibian context.

1.7. Empirical study

Because the study aimed to observe antibiotic usage and sensitivity patterns in Namibia, a descriptive approach was more suitable for the study. The study was conducted in four phases using a mixed method approach,

- Phase 1: Examined antibiotic consumption patterns;
- Phase 2: Studied antibiotic susceptibility data and compared with usage data from phase 1;
- Phase 3: Investigated patient knowledge and behaviour on antibiotics and their use;
- Phase 4: Prescriber behaviour and practices in Namibia.

The research methodology is discussed separately for each study phase.

1.7.1. Phase 1 – Antibiotic consumption patterns-retrospective drug utilisation review

As discussed in the introductory sections, the use of antibiotics globally is on the increase (CDC, 2013:11; Mollahaliloglu *et al.,* 2012:281; WHO, 2014a:1) and of concern due to its association with the development of resistance (Ashley *et al.*, 2011:1167; CDC, 2013:11; WHO, 2012:3). Not much is known about antibiotic use in Namibia. This phase of the study therefore aimed to quantify antibiotic usage in ambulatory patients in the private health sector of Namibia, in essence antibiotic use in community settings.

1.7.1.1. Study design

A study design is a plan on how the study is undertaken in order to sufficiently answer the research questions (Mouton, 2002:107). The study design is determined by the study aims and objectives, that is, the study design should be the most appropriate method to reach the study objectives.

In this phase an observational, descriptive research design was used by analysing retrospective medicine claims and wholesale data aimed at determining and describing prescribing patterns and quantifying antibiotic usage in a section of the private health sector of Namibia as a trend analysis over a period of four years.

Drug utilisation research is a research that describes the extent, nature and determinants of drug exposure with the aim of ensuring rational use of drugs in a population (WHO, 2003a:8-9) and thus increase our understanding of how drugs are used. The Academy of Managed Care Pharmacy defines drug utilisation review as "*structured, ongoing review of prescribing, dispensing and use of medication"* (AMPC, 2009:2).

Retrospective drug utilisation reviews are reviews that look back in time and analyse drug utilisation after the prescription has been dispensed and are useful for determining patterns in prescribing and dispensing drugs (AMCP, 2009:4). Truter (2008:95) describes these types of studies as serving the purpose of identifying trends in prescribing and dispensing practices.

Descriptive studies are non-experimental studies that seek to describe the variable of interest as it is observed (in its natural occurrence) (Botma, 2010:110; Van der Walt & Van Rensburg, 2011:103-104). According to Kamal (2011:44), descriptive studies describe what is going on or what exists.

This retrospective, descriptive study design was selected as it was deemed best suited for addressing the aim of this phase of the study, which is to describe patterns in antibiotic consumption within the private health sector of Namibia.

1.7.1.2. Data source

This retrospective descriptive study used the medicine claims database of one medical insurance fund administrator (similar to a pharmaceutical benefits management company) and sales data from a wholesaler in Namibia to investigate antibiotic usage from 1 January 2008 through to 31 December 2011.

Namibia has five medical suppliers one of which does not supply directly to pharmacies but to the other distributors and the other two do not carry antibiotics. Requests for data were sent to the remaining two wholesalers and only one agreed to participate in the study and provided data.

Both these sources, medicine claims database and wholesaler sales data, are reported among sources of data for drug utilisation review studies (WHO, 2003a:20). Furthermore, Ostrowski and Chung of the US Department of Health and Human Services, Agency for Healthcare Research and Quality, in their review of antibiotic data sources, record the advantages of these methods, among others, being ease of access and a combination of providing both aggregated and patient level data providing an indication of antibiotic exposure within a defined population/area (US Department of Health and Human Services). Coenen *et al.* (2013:2) asserted that in the absence of prescribing data, dispensing data (claims and sales) are the best proxy for antibiotic consumption.

Below, each data source is described individually in detail.

1.7.1.3. Medicine claims database

Medicine claims data are basically electronic records of all transactions that took place between a patient and a healthcare provider for which the medical insurer of the patient had to pay. It collects data for consultations, hospitalizations, procedures and pharmaceuticals claimed for by the healthcare providers (Ferver *et al.,* 2009:11). For this study, only outpatient medicine claims relating to antimicrobials were made available to the researcher by the medical fund administrator.

In their study to assess the capacity of a Pharmacy Benefits Management system – a system used to manage sales and purchases of drugs – Lima *et al.* (2008: abstract) found such a system capable of providing relevant information on profiles of prescriptions. Use of medicine claims/reimbursement data to determine drug usage and trends is not uncommon. In 2004, Stille *et al.* (2004:1207) used medicine claims data to evaluate the use of second line macrolides in paediatrics in the United States. In 2005, in Taiwan, Huang *et al.* (2005:827) conducted retrospective analyses to determine antibiotic prescribing in children using National Health Insurance data. A 6-year retrospective antibiotic consumption study was conducted in Ireland using Primary Care Reimbursement Services (PCRS) database (McGowan *et al.,* 2008). Similarly, Ferech *et al.* (2006:403) used reimbursement data for 12 countries when monitoring outpatient

antibiotic use in Europe. Also in Israel, Jaber *et al.* (2004:98) used the largest health insurance fund that provides health coverage to over 60% of the population to determine antibiotic prescribing practices.

The data fields contained in the database and that were used were:

- Sequential numbering as patient identifiers;
- Patient demographics (age and gender);
- Prescription information (number of items on prescription, dispenser type (whether pharmacist or medical doctor), location where item was dispensed and total cost of prescription); and
- Antibiotic information (name, strength, quantity, cost and NAPPI code). The NAPPI code, which stands for National Approved Product Price Index, is a unique identifier for each product that enables electronic data transfer on that product throughout the healthcare delivery system (MediKredit Integrated Healthcare Solutions, 2014).

In addition to the medicine claims database, data on bulk sales from the wholesalers were used to determine the extent of distributed antibiotics in the private sector. The bulk sales data were used to verify the results of the medicine claims database by comparing consumption from medicine claims database with bulk sales from the wholesalers' data by triangulation. For both databases, we requested only outpatient data such that data relating to hospitalised patients were not included in the data set sent. Furthermore, the public sector receives its medication from the Central Medical Stores and does not order medicines from the wholesalers. Therefore, the data set received from the wholesaler covers antibiotic sales only to the private sector. While these two data sources cover the same period, they were analysed separately and their respective results were compared.

1.7.1.4. Wholesale (sales) data

Sales data is the data that is collected during the sale of an item. In this study, sales data refers to data collected for sales of antibiotics by a wholesaler.

As with medicine claims data, the use of sales data as a surveillance method for antibiotic use is not uncommon. WHO (2012:19) indicates this data source as valuable. A study conducted by Gagliotti *et al.* (2009:1117) comparing medicine claims data and sales data in determining antibiotic use in Italy concluded that sales data are important for the estimation of systemic antibiotic use because medicine claims data do not cater for over-the-counter dispensing, a situation similar to Namibia. The European Surveillance of Antimicrobial Consumption (ESAC) in 2006 conducted a study on antibiotic use among outpatients in Europe (Ferech *et al.*, 2006:403). In this study, data from 13 countries were sales data. In 2004, a study was conducted in the United States (US) to compare consumption in the US with that reported by ESAC in 27 European countries. Data used for this study were also sales data (Goossens *et al.*, 2007:1091). Holloway and colleagues (2011:152) also used sales data as one of the data sources in a pilot project of surveillance of community antimicrobial use. Similarly, in 2004 in Delhi, India, Kotwani *et al.* (2009:556) used sales data as one of their data sources. Also, in determining non-hospital consumption of antibiotics in Spain during the 10-year period 1987-1997, sales data were used (Bremón *et al.*, 2000:396).

The data elements contained in the database were:

- Medicine code – a unique identifier given to each medicinal product (each strength and route of admin of a medicine is considered a different product and carries a unique medicine or product code);
- NAPPI code;
- Product category (trade or generic);
- Product name, active ingredient;
- MIMS classification – This is a Monthly Index of Medical Specialities classification system, which is similar to the ATC classification discussed earlier and classifies medicines according to their pharmacological action; and
- Total sales units per year – total units sold per antibiotic per year.

1.7.1.5. Study population

Population is the group of interest to the researcher – a set of people or items under consideration in a study (Van der Walt & Van Rensburg, 2011:123).

For the medicine claims database, the study population was the total number of prescriptions in the claims databases that contained one or more antibiotics for the period of 1 January 2008 to 31 December 2011 stratified by year.

For the sales database, the population was units of all antibiotics sold in the period between1 January 2008 and 31 December 2011 stratified by year.

Only prescription medicine claims containing systemic antibiotics for ambulatory patients were analysed. In the Global Perspectives of Antimicrobial Resistance chapter of the book Antimicrobial Resistance in Developing Countries by Sosa *et al.* (2010:4), Amábile-Cuevas argues that while resistance occurs among all organisms, it poses a distinct threat among bacteria because (i) antibacterial drugs abuse is higher than antifungal and antiviral agents, (ii) evolution of bacteria towards resistance exceeds that of other microbial, and (iii) bacteria and bacterial diseases are more abundant than other microbial therefore increasing the exposure to antibiotics.

In light of the above and the WHO guidelines on how to investigate drug use (WHO, 1993:16), other antimicrobials such as antivirals, anti-TB medications and antifungals were excluded from the analysis. Because the focus of the study is antibiotic use in community setting (among ambulatory patients), data on hospitalised patients were also excluded.

Furthermore, only prescriptions that were dispensed by the doctor or pharmacist were selected. This was because the nurses, who can also dispense, have limited scope of practice and therefore they can dispense only certain drugs and should they prescribe antibiotics, their prescription would not be honoured by the pharmacy or medical insurer. Also in private practice, there are very few (17) nurse-run clinics (SHOPS database, unpublished; NAMAF database, unpublished).

1.7.1.6. Study variables

Variables are measurable characteristics of the research study – they are factors that can affect or change the results of the study and are used to understand the differences in the study (Utts & Heckard, 2007:74)

From the medicine claims database, variables that describe both the users and dispensers were identified for analysis. For patients, these variables included age, gender and geographic distribution. These were selected in order to determine if antibiotic usage was influenced by any of these variables. A study conducted by Abasaeed in Abu Dhabi in 2006 and published in 2009 showed that antibiotic use in the community was affected by age and education level but not gender (Abasaeed *et al.,* 2009: 294).

For the dispenser, the variables dispenser type and geographic location were identified for analysis for the same reasons as mentioned for patients. Generic indicator, whether the medicine dispensed was a generic medicine or not, was another variable used.

Antibiotics usage was stratified according to these variables and comparisons of usage based on these variables were determined.

1.7.1.7. Study measures and measurement tools

In order to meaningfully measure drug use, it is important to have a classification system and a unit of measurement. Therefore, after the data were categorised according to the anatomical therapeutic classifications (ATC), the medicine usage and cost analysis measures were done. Usage measures included the frequency of antibiotics prescription by both type of antibiotic and antibiotic class/pharmacological group. Both total antibiotic usage (that is, overall consumption of all antibiotics) and specific antibiotic consumption, such as amoxicillin usage, were analysed. Consumption was reported as defined daily dose (DDD) per 1 000 population per day. For example, the analysis yielded the following results: total antibiotic consumption in 2008 was 28 DDD/1 000/day while amoxicillin usage was 2 DDD/1 000/day.

The ATC/DDD classification is a drug utilisation research tool which enables the presentation and comparison of drug consumption across different levels. The development of this tool stemmed from research conducted in the mid-1960s on drug consumption in six European countries which showed varied differences between countries in drug utilisation. This difference in drug consumption prompted the need for an internationally accepted classification system for drug utilisation research (WHO 2011:10 & 14).

In the ATC system, drugs are classified in groups at five different levels based on the body system or organ on which they act; as well as their therapeutic, pharmacological and chemical properties (WHO, 2011:15).

Table 1-2 below explains how drugs are classified in the ATC system using amoxicillin as an example.

Table 1-2: An example of ATC classification

Level	Definition	Example
1	Main anatomical group	**J** – Anti-infectives for systemic use
2	Pharmacological/therapeutic sub-group	J**01** – Antibacterials for systemic use
3	Pharmacological subgroup	J01**C** – Beta-lactam antibacterials, penicillins
4	Chemical subgroup	J01C**A** – Penicillins with extended spectrum
5	Chemical substance	Jo1CA**04**-Amoxicillin

Source: Created from WHO (2011b:165-170)

DDD is defined as the average maintenance dose per day for a drug used for its main indication in adults (WHO, 2013:22; WHO, 2003a:78). It gives an estimate of antibiotic consumption and it allows for comparison between countries and regions (WHO, 2003a:38; WHO, 2011:22).

Since the DDD definition emphasises “maintenance dose” and “main indication”, according to the WHO *2013 Guidelines for ATC Classification and DDD Assignment*,

when assigning DDDs to a product the following principles are considered (WHO, 2013:24–29):

- Dosage form – different dosage forms are assigned for different DDDs;
- Average adult dose used for the main indication of the medicine as reflected by the ATC code;
- Maintenance dose – this is preferred to the initial dosing;
- Treatment dose-this is preferred to the prophylaxis dose unless the product is used primarily for prophylaxis;
- The strength of the product;
- For combination product, DDD for the combination product should be equal to the DDD for the main active ingredient.

Based on these criteria, DDDs are signed for the different products and WHO produces a list of DDDs. The DDDs are reviewed every three years after inclusion in the list (WHO, 2013:29). The DDD method has limitations, one of which is that it cannot be used on children's medication (Zhang *et al.*, 2012: abstract; Truter, 2008:99; WHO, 2013:28).

Other drug utilisation metrics that were used include cost and volume. Cost measures included:

- Average cost per antibiotic item;
- Average cost per antibiotic containing prescription; and
- Antibiotic cost percentage contribution on a prescription
- Annual antibiotic cost as a percentage of total annual medicine claims.

Volume measured the quantities of antibiotic used-both individual antibiotics and antibiotic class. The volume looked at the total number of times that a particular antibiotic was prescribed (frequency and percentage) as well as the actual total quantities dispensed/sold for each antibiotic.

1.7.1.8. Data analysis

Prescribing patterns were analysed to determine both the trend and extent of antibiotic use in both medicine claims and sales databases. In order to facilitate this, data had to be first classified according to pharmacological classification and ATC systems. In the databases, the medicines were given using trade names. In order to classify them correctly as mentioned above, first the medicines were allocated generic names based on their active ingredient.

The strength, route of administration and the duration of the prescription were identified and used to calculate the prescribed daily dosage for each prescribed antibiotic. The WHO ATC/DDD list of 2013 was used to allocate DDD to each antibiotic.

The information on antibiotic use from the medicine claims database were verified by comparison with data on bulk sales from the wholesalers. As with the medicine claims data, both total and specific antibiotic "consumption" from wholesaler data were analysed. The analysis was also according to ATC system. In the context of the bulk sales, consumption referred to quantity of antibiotics sold by wholesalers to dispensing outlets.

Table 1-3 below shows the manipulation done to the data sets to facilitate analysis.

Table 1-3: Data elements added to the datasets to facilitate analysis

Data element added	Medical aid claims database	Wholesale database
MIMS classification	√	
ATC Classification	√	√
Generic name	√	
Product category	√	
Route of administration	√	√
Daily dosage	√	√
Prescription duration	√	N/A

All other statistical analyses conducted are reported under a separate section, section 1.8 below.

1.7.1.9. Reliability and validity

Medicine claims and sales data are appealing in conducting research because they are less costly than other sources, are anonymous and can be easily available.

Despite these advantages, these data sources have weaknesses that may affect their quality in certain studies (Burton & Jesilow, 2011:26; Ferver *et al.*, 2009:11; Truter, 2008:98). The main weakness being that they are not designed for research purposes and could therefore be wanting in the availability and accuracy of the data for research purposes (Ferver *et al.* 2009:12).

According to Ferver *et al.* (2009), some of the identified weaknesses in these data include:

- Under reporting of claims;
- Coding error – entering the wrong code (medicine or disease) on the database;
- Fraud – claims based on events that did not occur;
- Upcoding – claiming for a more expensive treatment than that offered to a patient;
- Limitations in level of detail in the data base – this refers mainly to clinical detail.

Given what this study aims to answer, none of the weakness indicated above are of particular concern on the basis that the medical fund administrator follows a stringent process to ensure quality of the medicine claims to facilitate reimbursement. The prescription is approved electronically at the time of dispensing – that is before the completion of dispensing, the pharmacists electronically submit the dispensing authorisation request, the administrator system then responds electronically with an authorisation or rejection. This system ensures that incorrect patients and unapproved medicines are rejected prior to dispensing.

Secondly, physical medicine claims must be submitted. These medicine claims contain a copy of the prescription claim as well as a copy of the actual prescription. The

medicine claim is signed by the patient and dispensing pharmacist. This step minimises the risk of medicines that were not supplied being claimed for. Furthermore, it also allows the medical aid administrator to cross check if the medicine issued was the one prescribed.

Finally, the medical aid administration also conducts routine audit of sales and prescriptions prior to paying out the claim.

For the wholesale, barcodes are used for scanning goods as they are sold. The barcode is linked to the medicine name, description and code. This minimises the risk of a wrong item being entered onto the system.

The data were received from the suppliers on Microsoft Excel®2010 format and the only manipulation to the data were cleaning the data (ensuring that only antibiotics and no other antimicrobials are used for analysis) and adding the ATC and DDD classifications as per WHO 2013 report. This limited threats to internal validity, that is, the degree to which the outcomes of the study could be attributed to the manipulated independent variable (Van der Walt & Van Rensburg, 2011:99).

The fact that data were received from only one medicine claim database and one wholesaler posed a threat to external validity, meaning that the results could only be generalised to the specific database used and the specific study population (Van der Walt & Van Rensburg, 2011:101). However, this was catered for by using sales data to compare with claims data.

Burton and Jesilow (2011:28) conclude that to improve validity, medicine claim data should be compared with other sources data.

1.7.1.10. Ethical considerations

Ethical clearance for this study was obtained from the Research Ethics Committee (Human), Faculty of Health Sciences, North-West University (Ethical clearance number NWU-00028-13-s1). Additionally, permission to use the data for the study was provided along with the data by the participating medical insurance providers, their medical fund administrator and the wholesaler.

To protect patient and healthcare provider confidentiality, data from the medicine claim database was anonymised (that is, no patient or provider identifiers were given to the researchers). Furthermore, the anonymity of the provider of the data were kept secret and is not mentioned throughout the report.

1.7.2. Phase 2: Determination of antimicrobial susceptibility

The microbiology laboratory is an important partner in addressing antimicrobial resistance due to its ability to identify pathogens that cause infections and antimicrobials that are effective against these pathogens (WHO, 2003b). According to the WHO (2012:20, 26), a combined strategy of surveillance for antibiotics (that is, using both consumption and resistance data) provides a better understanding of the relationship between usage and resistance. Accordingly, this phase follows the previous phase and uses laboratory data to determine the linkages between antibiotic usage and resistance.

This sub-section describes how laboratory data were used to determine antibiotic susceptibility trends in Namibia.

1.7.2.1. Study design

A cross-sectional study is a study design that is used to determine the prevalence of a phenomenon at a specific point in time. In a retrospective study, one looks at a phenomenon after it has occurred (Mann, 2003:56-57). The purpose of this phase of the study is to determine susceptibility patterns of antibiotics over the period from 2007 to 2011 in Namibia. Finch (1998:126) suggests that antibiotic resistance is a function of time and use. Finch (1998) further suggests that cross sectional surveys are adequate to measure resistance trends. Numerous studies have been conducted that show the relationship between antibiotic use and the development of resistance over time (Bergman *et al.*, 2006:3647-3649; Gallini *et al.*, 2010:265; Hsu *et al.*, 2010:1175–1176; Hsueh *et al.*, 2005:469-472; Kritsotakis *et al.*, 2008:752; Mohamat *et al.*, 2005:303-306; Vernaz *et al.*, 2011:933). In light of the above studies, a retrospective, cross-sectional design was found most appropriate for this phase.

1.7.2.2. Data source

Aggregated routinely collected susceptibility data from the local pathology and medical laboratory was used for this phase of the study. Namibia has two main laboratories with one having more presence in the public sector than the other. The laboratory selected covers 80–90% of all private patients, as the focus of the study is the private health sector. The laboratory that has a very small presence in the private sector was therefore excluded from the study. Data from the laboratory are collected routinely and aggregated every six months. The laboratory did not have data for 2007 thus making the intended analysis of the period 2007 to 2011 impossible. The available data from the laboratory for this study was from 2001 to 2011 with a gap (missing data) between 2005 and 2010.

Antibiotic susceptibility results that were used in this phase were from antibiogram surveillance where routine bacterial isolates are collected and summarised. An antibiogram is the result of a laboratory testing for the sensitivity of an isolated bacterial strain to different antibiotics which are organised and reported cumulatively in a table (CDC, nd:2). Similarly, the laboratory compiles these data from the Namibia private health sector to assess regional susceptibility and monitor trends over time. Antibiogram data are presented as percentage susceptible isolates for different pathogen-antibiotics combinations as shown on the example below (see table 1-4).

Table 1-4: Example of aggregated antibiogram (hypothetical data)

		% susceptible isolates		
Organism	Isolates	Ampicillin	Amoxi-clav	Ciprofloxacin
E. coli	203	21	32	70
K. pneumoniae	79	22	22	65
P. auruginosa	36			50

In identifying sensitivity of pathogens, the laboratory has rigorous processes and protocols that it follows. When samples are received they are checked for acceptability. This includes checking if time of specimen collection is appropriate, for instance, urine

samples should be collected and tested within 2 hours. After the screening process, the following procedures (figures 1-1 to 1-3) are followed, according to the source of the culture:

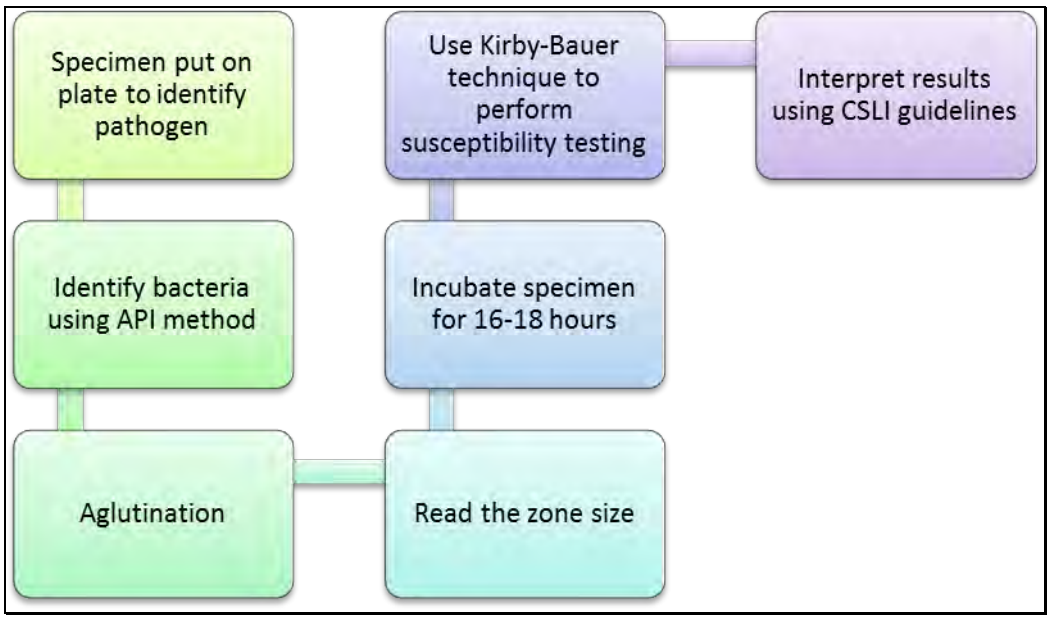

Figure 1.1: Antibitioc susceptibility testing procedure for stool Specimen

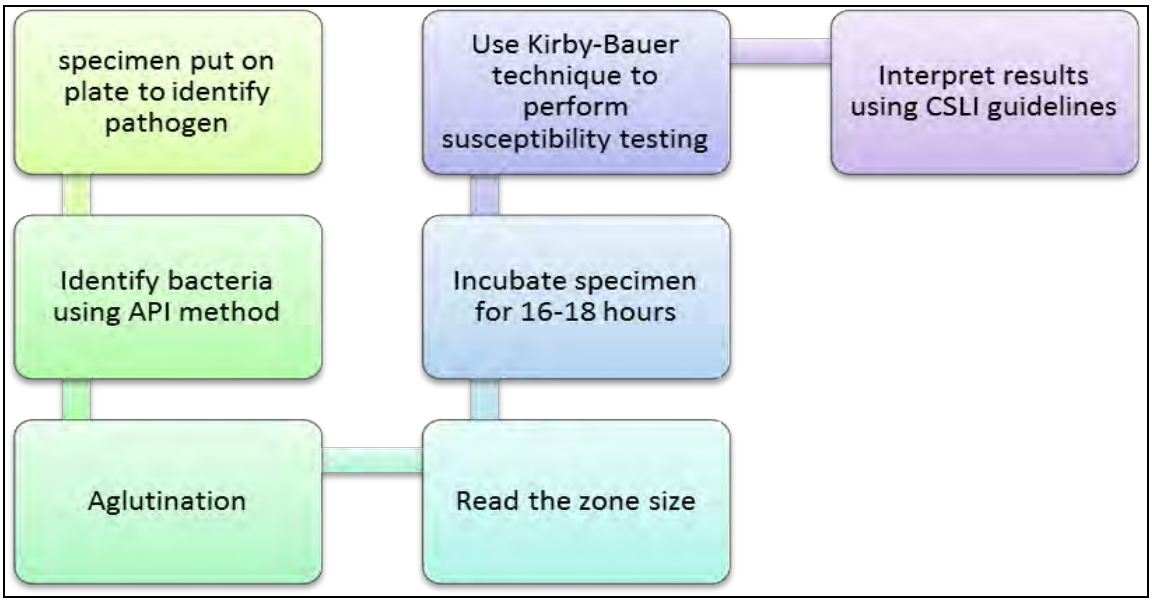

Figure 1.2: Antibiotic susceptibility testing process for urine Specimen

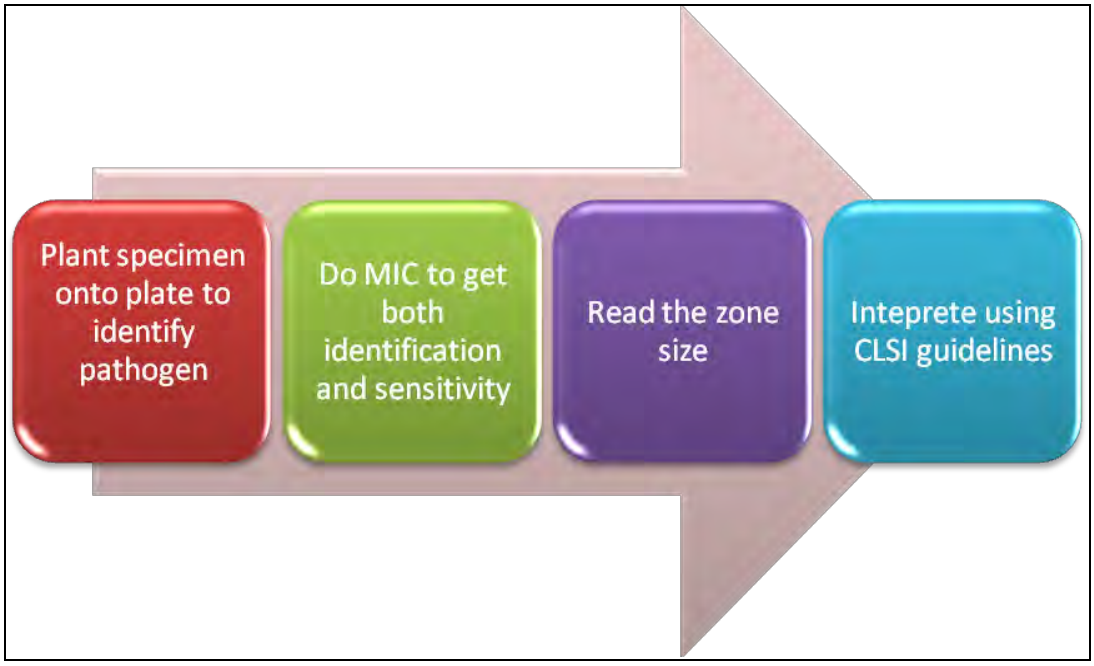

Figure 1.3: Antibiotic susceptibility testing process for sputum Specimem

The results are then entered and recorded on Meditech® and antibiogram prepared.

The use of antibiograms for resistance monitoring was found to be as effective as active surveillance methods (Stein,*et al.*, 2003:211,215). A similar conclusion is reached by

Van Beneden *et al.* (2003:1090), who also indicates that such methods are less costly and less time-consuming. Furthermore, Orsi *et al.* (2011) argues that this is the simplest form of resistance surveillance. "*This method is particularly useful to detect the emergence of new multi-drug resistant organisms not previously detected, either within an individual healthcare facility or community wide. Furthermore, the data may be used to prepare antimicrobial susceptibility reports describing pathogen specific prevalence of resistance among clinical isolates*." The WHO (2012:14) also recognises the data from routine diagnostic laboratories as primary data suitable for antimicrobial resistance surveillance, while the United States Centres for Disease Control and Prevention (CDC) reported antibiograms as adequate at estimating prevalence of resistance (CDC, nd:3)

These data can further be used to assess effects of interventions designed to reduce antibiotic resistance through judicious antibiotic use.

A letter of permission and request for data were sent to the laboratory (refer to annexure A)

1.7.2.3. Study population

The laboratory provided the data as aggregated susceptibility data for each pathogen. The study population was therefore the aggregated susceptibility data from the laboratory for the period 2010 to 2011.

These data contained only the pathogens tested, number of isolates for each pathogen and the antibiotic panel that the various pathogens were tested against. These are the only variables that were analysed.

The study measure that was used was the percentage susceptibility of each pathogen to each individual antibiotic. Since in this phase the study sought to test for any association between antibiotic usage and resistance, the antibiotic usage measures of DDD/1 000 population per day described in phase 1 was also used in presenting the results.

1.7.2.4. Study variables

Based on the information received from the laboratory, the variables that were studied in this phase were the pathogen, the number of isolates and the antibiotic panel for each pathogen reported on. The pathogen was the independent variable.

1.7.2.5. Study measures

The first study measure used in this phase of the study was the percentage susceptibility of the pathogen to the each antibiotic on the panel. This was to determine the level of antibiotic resistance to key antibiotics.

The second measure used was the DDD/1 000 population per day. This is because the results from phase 1 of the study were used to determine any association between antibiotic usage and reported resistance.

1.7.2.6. Data analysis

Statistical methods to test for association were used. Firstly, histograms and linear regression model were used to test the distribution of the data so as to inform what statistical test would best be suited to test for correlation.

Full description of tests carried out is discussed under the section 1.8 below.

1.7.2.7. Reliability and validity

The data for the study were obtained directly from the laboratory database and thus no direct manipulation of the data were made by the researchers.

Threats to validity expressed by the CDC (nd:12) are:

- Inclusion of non-sterile isolates and multiple isolates from a single patient – these are likely to increase the overall percentage resistant; and
- Use of different testing methodologies;

The laboratory follows a stringent process of ensuring that the correct and only sterile samples are included for resistant testing. Since it is one laboratory, the same testing

method (already described under data sources) is used, therefore, there is no chance of variations in methodology.

Seeing that data were obtained from only one laboratory, external validity (extent to which the results can be generalised) is affected, implying that results can only be generalised to the specific laboratory used and the population serviced by the laboratory. However, for this study, the results can still be generalised to the private patient population since the selected laboratory covers about 80% of the private health population.

1.7.2.8. Ethical considerations

Ethical clearance for this study was obtained from the Research Ethics Committee (Human), Faculty of Health Sciences, North-West University (Ethical clearance number NWU-00028-13-s1). Additionally, permission to use the data for the study was requested (see copy of letter in annexure A) and given by the laboratory.

Data provided are aggregated data and have no linkages to actual patients or practices that requested for laboratory diagnostics and therefore confidentiality of patients is preserved.

1.7.3. Phase 3: Determination of patient knowledge and behaviour regarding antibiotic use

The standard of antibiotic use is determined by both prescribers and users, therefore the development of resistance can be a factor due to inappropriate use by prescribers or users (Franco *et al.*, 2009:5; Okeke *et al.*, 1999:19). Consequently, this study also focused on the behaviour of both prescribers and users as well as clinical practices of prescribers. This particular phase focused on antibiotic users and the next phase on prescribers (medical doctors).

The idea that antibiotic resistance is strongly associated with inappropriate antibiotic use is well accepted. Okeke *et al.* (1999:19-20) argue that the drivers for the development of antibiotic resistance include inappropriate use in the community,

sentiments that have been shared by various other authors (Buke *et al.*, 2005:136; Hashemi *et al.*, 2013:385-385; Kotwani & Holloway, 2011:1; Kotwani *et al.*, 2012:308).

The role of patients or end-users' contribution to the development of resistance has been well-documented. Davey *et al.* (2002:63) conclude that patients, as end-users of antibiotics, are essential in the control of antibiotic use and development of resistance. They further suggest that patient behaviour associated with attitude, knowledge and beliefs can influence prescribing. Similar thoughts were shared by Belongia *et al.* (2002:349), who concluded that the general public had misconceptions about antibiotics and that their attitudes and expectations were contributors to inappropriate antibiotic use and therefore the development of resistance. Harbarth and Samore (2005:794) classify the determinants of antimicrobial resistance into four groups-one of which is characteristics of the patient population including their knowledge and attitudes. They further note that social views on infectious diseases and antibiotics greatly influence the use of antibiotics (Harbarth & Samore, 2005:796).

In its report on *Global Strategies for Containment of Antimicrobial Resistance*, the WHO (2001:21-22) also highlights patient-related factors as major contributors to the development of resistance. Specifically, factors related to unnecessary use of antibiotics even when not indicated and poor adherence to antibiotics are highlighted as concerns.

It is therefore important to determine what the community understands about antibiotics and how they tend to use them. With this in mind, this section of the study therefore examined the Windhoek community's understanding and behaviour in relation to antibiotics and their use.

1.7.3.1. Study design

The study was a descriptive, cross-sectional community-based study conducted between 1 March 2013 and 30 June of 2013 in Windhoek. Cross-sectional design is best suited for studies to determine knowledge, attitudes and practices and this design has been widely used for such studies (Abasaeed *et al.*, 2009:492; Al-Dosari, 2013:40; Auta *et al.*, 2013:1088; Afolabi *et al.*, 2014:103; Andre *et al.*, 2010:1292; Bala *et al.*, 2013:429; Belkina *et al.*, 2014:428; Buke *et al.*, 2005:136; Kim *et al.*, 2011:743; Kheder

& Ayed, 2013:752; Mohamed *et al.*, 2014:73; Mitsi *et al.*, 2005:439; Napolitano *et al.*, 2013:2; Oh *et al.*, 2011:339; Panagakou *et al.*, 2011:61; Parimi *et al.*, 2002:12; Rousounidis *et al.*, 2011:3247; Shehadeh *et al.*, 2011:126; Skliros *et al.*, 2010:58; Suiafan *et al.*, 2012:764; Vanden Eng *et al.*, 2003:1128; You *et al.*, 2008:154; Yu *et al.*, 2014:114). The study is purely descriptive and aims to quantify the knowledge, attitudes and behaviour of the community as it relates to antibiotics (Maree, 2010:155; Strudwig & Stead, 2001:8).

1.7.3.2. Study population

The focus of the study was in Windhoek in Namibia. Windhoek is the economic hub of Namibia and most private patients on medical insurance and private doctors are working in Windhoek. According to the City of Windhoek, approximately 268 000 people reside in Windhoek, corresponding to 13% of the total population of Namibia (City of Windhoek, unpublished). In the greater Windhoek area, over 30% of individuals are enrolled in a medical aid fund (Janssens *et al.,* 2008) and therefore receive their healthcare primarily from the private sector. Windhoek therefore represents a large proportion of private health sector usage in the country.

According to NAMAF figures, there are approximately 466 doctors in the country of which 52% are located in Windhoek (NAMAF 2011 Conference presentation, unpublished). These statistics also show that only 15% of specialists are outside of Windhoek therefore most patients requiring specialist opinion will likely see the specialist in Windhoek.

Given the healthcare set up in Namibia, it was decided that the best way to collect the data would be through the pharmacies. A letter of support was then sent to the Pharmaceutical Society of Namibia (PSN) and subsequent meeting to discuss the study and the data collection procedure was held (a copy of the letter is attached in annexure B). PSN then forwarded the letter to all Windhoek pharmacies encouraging participation in the study. The community pharmacists that indicated interest were individually visited to discuss the data collection procedure, in particular the age limitations for participation

in the study (that is, to only get information from patients 18 years and older), the need to gain consent before participation and that the questionnaire is self-administered.

The same principles as outlined in “How to Investigate Drug Use” (WHO, 1993:26; Holloway *et al.*, 2011:153) of collecting at least 30 survey forms from 20 facilities were used. Thus at least 600 surveys from patients were anticipated. Twenty pharmacies were targeted. A two-stage random cluster sampling protocol was used to increase the chances of a representative sample (Maree, 2010:175). Windhoek was divided into different areas and seven areas were randomly selected. Community pharmacies were then randomly selected from the randomly selected clusters to ensure participation from different parts of the city. Most of the community pharmacies were given 30 questionnaires and very high volume pharmacies who indicated interest were issued 40 50 questionnaires that were collected over a month. In addition to the structured questionnaire, the community pharmacists were given informed consent forms to be completed by the respondents.

Adult patients (18 years and older) visiting community pharmacies in Windhoek were included in the study. This age group was selected because legally, it is the age group that can give consent.

1.7.3.3. Research instruments and administration

This section details how the research instruments and questionnaires were developed and administered in order to collect the data for the study.

1.7.3.4. Development of questionnaire

The survey was conducted through the use of self-administered questionnaires (see Annexure 2). The advantages of this method of data collection are that it is simple, inexpensive and quick and easy to administer (Nunes *et al.*, 2009:179) hence it was chosen.Surveys and questionnaires have been used successfully in the past to determine antibiotic use and behaviour within the community. In 2008, Yah and colleagues (2008:82) performed surveys through use of questionnaires to determine patterns of antibiotic usage by adults in Benin City, Nigeria. Similarly, Parimi *et al.*

(2002:12), You *et al.* (2008:154), Andre *et al.* (2009:1292), Chen *et al.* (2005:53), McNutty *et al.* (2007:i64), Vanden Eng *et al.* (2003:1129) and Shehadeh *et al.* (2011:126) used questionnaires to conduct both telephone and face-to-face surveys to determine general public prescriptions knowledge, attitude and behaviour on antimicrobial use in Trinidad and Tobago, Honk Kong, Sweden, Taiwan, United Kingdom, United States and Jordan, respectively. Furthermore, self-administered questionnaires were used by Oh *et al.* (2010:339) and Suifan *et al.* (2012:764) to determine knowledge, attitude and behaviour related to antibiotics by the community in Malaysia and Jordan, respectively.

In their chapter on questionnaire design, Eiselen *et al.* (2005:2) as well as Neuman, (2014:345-346) describe the advantages of self-reported questionnaires.

- They are more cost effective to administer than face-to-face interviews;
- They are easy to administer and to analyse;
- They reduce the possibility of interviewer bias; and
- They are preferred by respondents as they are perceived to be less intrusive than other forms of survey. This makes respondents more truthful in their responses.

Despite the fact that questionnaires are widely used for data collection, they have disadvantages that should be borne in mind when designing the questionnaire. The main disadvantages as identified by Eiselen *et al.* (2005:2) and Neuman (2014:345-346) are:

- The response rate tends to be low. This can be minimised by making the questionnaire short, easy to follow and easy to complete;
- The researcher is not able to clarify for the respondent;
- Phrasing of questions may not be clear to the respondent and therefore lead to errors in response (Nunes *et al.,* 2009:179); and
- The wrong person other than the intended respondent might fill the questionnaire.

The following process was followed in designing the questionnaire:

- **Determination of questions**

The questions to be asked were determined based on the aims and objectives of the study. The criteria to be measured were determined and questions that would best address the identified criteria were chosen. A literature review was conducted to identify studies with similar objectives that were conducted elsewhere to see examples of questions and questionnaires. All the studies listed under the section “the development of questionnaires” employed questionnaires to determine population knowledge and attitudes. These, with the exception of Suaifan *et al.* (2012:764) and with the addition of Pechere (2001:s171) were used in the review for the design of the questionnaire. This was to make sure that the standard of the questionnaires was on par with other researchers in the field.

- **Design of the questionnaire**

In designing the questionnaire, the above listed advantages and disadvantages were considered together with the type of respondent anticipated. Because the survey was to be done on respondents across all levels of education, it necessarily had to be simple. The simplest survey in understanding the patient’s knowledge about drugs is to enquire about the medicines they are taking and their understanding on how to use them, (Truter, 2008:97). The questions were designed in such a way as to ensure that they were clear, unambiguous, concise, easy to comprehend and easy to complete.

The questionnaire contained both open and close-ended questions. The open-ended questions required mainly one word responses (such as symptom and diagnosis).

Difficult words such as “diagnosis” were used and explained in layman terms “such as, what is your sickness” to ensure that all respondents would understand.

The questionnaire was divided into two sections – demographic information and knowledge of antibiotics. The latter section contained questions aimed at antibiotic usage, how antibiotics were obtained, reason for use, compliance and knowledge on how and when antibiotics should be used. The questionnaire emphasised respiratory tract infections, especially the common cold. It is a documented fact that the biggest prescription of antibiotics in primary outpatient care settings is for respiratory tract

infections, which include pharyngitis, common cold, rhinitis, cough and acute sinusitis (Adriaenssens, 2011:764; Goossens, 2007:1; Furgerson, 2004:40; Jaber, 2004:97; Rousounidis, 2011:3247; Van der Velden, 2013:319). Although these infections have a viral aetiology, antibiotics are widely prescribed for their treatment. Furthermore, it has been reported that patients believed that antibiotics were necessary for treatment of respiratory infections (Alzoubi, 2013:480; Pechere, 2001:S171; Rousounidis, 2011:3247; Van der Velden 2013:319).

In all, the questionnaire contained 14 open and close-ended questions (mainly with dichotomous questions and one multiple choice question). The questionnaire started with a brief description of the study – the purpose and information on the voluntary nature of the study.

The questionnaire was developed in English and translated into Afrikaans-the two common languages used in Windhoek. The Afrikaans questionnaire was validated by back translation into English by a different translator.

- **Peer review**

Once the questionnaire was completed, it was given to experienced researchers, colleagues and health professionals for their review and input. The peer reviewers commented on the content of the questionnaire, the flow of questions and ambiguity in questions and responses. They also provided input on the lay-out, sequencing of the questions, length of the questions (are there questions that are too long and should be split?) and the length of the questionnaire. Comments from the peer review were used to improve the questionnaire prior to piloting.

- **Piloting**

The piloting was conducted to detect any flaws in the questions and, to determine the ability of potential respondents to understand and complete the questionnaire. Katzenellenbogen *et al.* (2004:89) suggest that a questionnaire should be pre-tested using between five and 20 individuals who do not form part of the final study sample. In accordance to this, the questionnaire was pre-tested among 20 randomly selected

individuals. Three additional questions were added to the questionnaire for piloting purposes. The respondents were requested to comment on:–

- The length of the questionnaire;
- Whether the questions were clear, unambiguous and understandable; and
- How long it took them to complete the questionnaire?

From the pilot study, respondents were found to be able to understand and answer most of the questions on the questionnaire provided. The time taken to respond to the questionnaire was reported to be between 3 and 6 minutes. The findings of the pre-test were used to finalise the questionnaire. (A sample of the questionnaire is attached in Annexure D)

1.7.3.5. Reliability and validity

Reliability refers to the accuracy or precision of the instrument, that is, the extent to which independent administration of the same instrument yields the same or similar results under comparable conditions (Curtis & Curtis, 2011:13; David & Sutton, 2011:268 – 269; De Vos, 2004:166-168; Mouton 2002:144; Struwig & Stead, 2001:130). Some of the factors that have been reported on to affect reliability of the questionnaire include (CDC, 2003:14-18):

- Ambiguity of questions (such as negative phrasing of questions or asking multiple concepts in one question);
- Vague questions – can lead to inconsistencies in interpreting the meaning of the question;
- Language that is difficult to understand; and
- Lack of clarity on how the question should be answered.

A similar list was provided by Struwig and Stead (2001:130-131), who further suggested that to prevent these errors, the instrument should be comprehensive and clearly understood. David and Sutton (2011:268) suggest that to improve the reliability of the questionnaire, it should be well constructed and piloted; and existing questions from reputable researchers should be used in constructing the questionnaire. As already

discussed above, the questionnaire was reviewed and piloted to ensure that it was clear and unambiguous. All words that were deemed difficult were explained and also written in “lay man terms”.

Validity, on the other hand, refers to the extent to which the instrument actually measures the concept in question and measures it accurately (De Vos, 2004:166-168; Maree, 2010:216).Validity comprises internal and external validity. External validity refers to the extent to which the results of the study can be generalised to the entire population. It is affected by sampling (Struwig & Stead, 2001:136). In this phase, the sample size and methodology used was such that the results could be generalisable to other populations. A two-stage random cluster sampling protocol was used to increase the chances of a representative sample (Maree, 2010:175). Pharmacies were divided into seven clusters, according to geographic location to ensure participation from different parts of the city in order to facilitate generalization of the results.

Below are the types of validity and how they were provided for in this research.

Face validity – this simply refers to the extent to which the instrument measures what it is intended to measure (Curtis & Curtis, 2011:211; David & Sutton, 2011:268; Katzenellenbogen *et al.*, 2004:92; Neuman, 2014:215; Shuttleworth, 2009). Maree (2010:127) and David and Sutton (2011:268), suggest that to provide for this, the instrument should be reviewed by experts in the field. As already discussed in the questionnaire development section above, the instrument was peer reviewed prior to pilot and field work.

Content validity – this refers to how the instrument covers the theoretical content of the construct it is set to measure, that is, how much the measure represents every aspect of the construct, (Curtis & Curtis, 2011:211; David & Sutton, 2011:268; Katzenellenbogen *et al.*, 2004:92; Neuman, 2014:216; Shuttleworth, 2009). In this study, representative questions that reflect the use, knowledge and attitudes/practice of respondents towards antibiotics were selected. These were in line with what other researchers had already done and were peer reviewed.

Criterion-related validity – this refers to the degree to which the instrument correlates to other instruments known to measure the same construct (Curtis & Curtis, 2011:211; David & Sutton, 2011:268; Mouton, 2002:128; Neuman, 2014:216; Shuttleworth, 2009). Because the questions used in the questionnaire were comparable (similar) to those in other studies of a similar nature, criterion validity was assumed. Eleven other studies measuring community knowledge, use and practice with respect to antibiotics were reviewed and used to design the questions for the study (Andre *et al.*, 2009:1292; Chen *et al.*, 2005:53; Oh *et al.*, 2010:339; McNulty *et al.*, 2007:i64; Parimi *et al.*, 2002:12; Pechere, 2001:s171; Shehadeh *et al.*, 2011:126; Suiafan *et al.*, 2012:764; Yah *et al.*, 2008:82; You *et al.*, 2008:154; Vanden Eng *et al.*, 2003:1129).

Construct validity – this refers to how well the instrument measures the theoretical construct it was intended to measure, that is, it must measure only what it was intended to measure, (Agarwal, 2011:1; Curtis & Curtis, 2011:154; David & Sutton, 2011:268; Mouton, 2002:128; Neuman, 2014:215; Shuttleworth, 2009). Radhakrishma (2007) in the article "Tips for developing and testing questionnaires/instruments" suggests that validity of the questionnaire is established by expert review as well as piloting. Shuttleworth (2009) also suggests that a pilot establishes the strength of the questionnaire. Furthermore, Agarwal (2011:3) in the study "Verifying survey items for construct validity" used three steps, the first being expert review and the second and third being testing of the questionnaire by "judges". Similarly in this study, the questionnaire was reviewed by experts (pharmacists, medical doctor and researcher) and was also piloted and input from the piloting used to finalise the instrument.

1.7.3.6. Practical administration of the questionnaire

Data were collected between 1 March 2013 and 30 June 2013. After the community pharmacies willing to participate in the study were identified, they were visited and the pharmacist identified as the person to hand out the questionnaire and explain it to the patients. The researcher and pharmacist went through the questionnaire together to ensure same understanding.

At the community pharmacies, patients were asked if they were willing to participate in the study and those indicating willingness were given the questionnaire and the informed consent form. The inclusion criteria (that they should be 18 years and older to participate) and the anonymity of the survey were explained to them. Patients completed the questionnaires at the community pharmacy while waiting for their prescriptions to be filled. Some patients insisted on taking the questionnaire home and these did not return the questionnaires.

Community pharmacists were called and/or visited weekly by the researcher to establish if there were any concerns with the data collection process. In some instances, the pharmacists were too busy to “administer” the questionnaire and this resulted in extension in the data collection period from the originally proposed one month to three months.

At the end of the data collection period, not all community pharmacies had obtained the required number of responses.

1.7.3.7. Data analysis

In order to facilitate analysis, variables to be analysed need to be determined. Variables are the "things" that the researcher collects data on in order to answer the research questions (Maree, 2010:147). Variables to be analysed were identified at the onset of the study. Because the study aimed to understand knowledge and practices of community members regarding antibiotics, the following independent study variables were used:

- Age;
- Gender;
- Employment status;
- Member of medical aid; and
- Education level.

These variables were also collectively clubbed as demographics and they enabled us to describe the respondents. In addition to these, the following measures (dependent

variables) were used to determine the behavioural patterns of respondents with respect to antibiotic usage:

- Antibiotic usage in the past year;
- Method of obtaining antibiotic;
- Time of antibiotic stoppage;
- Self-request for antibiotics; and
- Whether information on how to use antibiotic was given or not.

Additionally, the five knowledge and practice questions were also analysed against the listed variables.

A data entry questionnaire was designed on Epi-Info™ 7. Three questions on the questionnaire required coding of responses. The responses were entered onto Excel® and coded there before creating the Epi-Info™ 7 data entry questionnaire. The completed questionnaires were entered onto Epi-Info™ 7. The questionnaires were numbered and filed in the way they were entered onto Epi-Info™ 7. After each data entry session, the batch entered was checked against the entry made onto Epi-Info™ 7. Additionally, every tenth questionnaire was entered onto Excel®. The Excel® entries were printed out and compared with the entries made onto Epi-Info™ 7. Completed questionnaires were marked and filed.

Questionnaires that were completed with age under 18 years old were removed from the sample.

Data were then exported from Epi-Info™ 7 onto Excel® where the data were cleaned. The data were then imported onto SAS version 9.1.3 (SAS Institute, Cary, NC) for analysis. Descriptive statistics of frequencies (numbers and percentages) were used to describe and summarise the data. For inferential statistics, all results were regarded as statistically significant when $p \leq 0.05$. The practical significance of the results was computed when the *p*-value was statistically significant ($p \leq 0.05$). Variables (age, gender, education level, and employment) were expressed using descriptive statistics such as frequencies (n) and percentages (%). The Chi-square test (X^2) was used to determine if an association existed between proportions of two or more groups. The

Cramer's V statistic was used to test the practical significance of this association (with Cramer's $V \geq 0.5$ defined as practically significant). More detail on statistical analysis is reported under section 1.8 *Statistical Analysis* below.

1.7.3.8. Ethical considerations

Ethical clearance for this study was obtained from the Research Ethics Committee (Human), Faculty of Health Sciences, North-West University (Ethical clearance number NWU-00028-13-s1). Additionally, only pharmacies that were willing to participate were included in the study.

The study was anonymous to ensure confidentiality. Respondents were requested to give consent to undertake the study. (A copy of the consent form is attached in annexure C).

1.7.4. Phase 4: Determining from the perceptions of private doctors (general practitioners and specialists) their behaviour and clinical practice in prescribing antibiotics

As already discussed in the preceding sections, the relationship between antimicrobial resistance and consumption is well documented. In a country like Namibia, where the sale of antibiotics is restricted by law, that is, antibiotics can only be sold if prescribed by a medical doctor, (Medicines and Related Substances Control Act, 13 of 2003), the consumption of antibiotics could be inferred to be linked to prescribing practices. Furthermore, studies conducted have strong evidence of association between antibiotic prescribing in primary care and the development of resistance (Costelloe *et al.*, 2014:46; Costelloe *et al.*, 2010:11).

In their description of determinants of antimicrobial resistance, Harbath and Simore (2005:794-795) list the second category of determinants as linked to prescribing practices of physicians. Larson (2007:439) also indicates prescriber practices as a factor associated with antibiotic resistance in the community. Therefore, understanding

the attitudes and practices of prescribers can help in determining appropriate interventions to improve antimicrobial usage patterns.

1.7.4.1. Study design

As with the previous phase of the study, this phase is also a cross-sectional observational study because this method is aimed at assessing current practice over a short period of time. Because the researchers were observing the practice of the prescribers at a specific point in time and without influencing the study environment, a cross sectional design was deemed the best fit (Mann, 2003:56).

This phase builds on the usage analysis gathered in phase 1 and phase 3 of the study. Whereas phase 1 provides information on what was being used, to what extent and at what costs, and phase 3 provides information of how the patients use antibiotics. This phase attempts to answer the question “why antibiotics are being used” and “how are they prescribed”, determine the appropriateness of the use and understand prescribing patterns of prescribers. To answer these questions, phase four employed a survey to assess clinical practice and behaviour of prescribers.

1.7.4.2. Study population

The study population comprised all doctors who are members of the two medical associations in Namibia. Namibia has only two medical associations to which majority (at least 70%) of the doctors belong.

In accordance with the Namibian law (Medicines and Related Substances Control Act, 13 of 2003), only doctors and nurses are authorised prescribers. The study focused only on doctors, as the majority of the prescribers in the country. Nurses also have a limited scope of practice and a limit to what they can prescribe and/or dispense (Act 13 of 2003). Also, there are few independently practising private nurses.

1.7.4.3. Research instruments and administration

As with the previous phase, a questionnaire was used as the data collection instrument for this phase of the study. The survey employed a self-reporting or self-administered

questionnaire but unlike the previous phase, this questionnaire was web-based. Advantages and disadvantages of self-reporting questionnaires have already been discussed in phase 3, therefore they will not be discussed again here.

1.7.4.4. Development of questionnaire

Use of survey questions to determine doctors' perceptions, knowledge, beliefs and attitude has been employed successfully. Butler *et al.* (1998) use structured interviews to understand the culture of prescribing antibiotics for sore throat. Similarly, Paluck *et al.* (2001:523) use self-reported survey questionnaires to assess prescribers' practices and attitudes towards giving children antibiotics. In 2002, Wester *et al.* (2002:2210) conducted a similar study in Chicago to determine physician's perceptions on antibiotic resistance. Srinivasan *et al.* (2004:1452) also use surveys to assess the knowledge, attitude and beliefs of doctors in various specialities at Johns Hopkins Medical Institutions. Even in recent years similar studies were conducted in Brazil (Guerra *et al.*, 2010:60), France (Lucet *et al.*, 2011:937), France and Scotland (Pulcini *et al.*, 2010:81), India (AfzalKhan *et al.,* 2013:1614), Peru (Garcia *et al.,* 2011:2) and the United States of America (Stach, 2012:191). In Africa, similar studies have been conducted in the Democratic Republic of Congo (Thriemer *et al.*, 2013:2), Lesotho (Adorka *et al.,* 2013:345) and Sudan (Kheder, 2013:348).

The same process that was followed in designing the research instrument discussed in phase 3 (that is, determining questions to be asked, designing the lay-out, peer review and piloting) was followed.

In determining the questions to ask, an extensive literature search of similar studies was conducted. Literature was also consulted to identify common infections presented at outpatient settings (Adriaenssens, 2011:764; Chandy *et al.*, 2013:233; Goossens, 2007:1; Jaber, 2004:97; Murphy *et al.*, 2012:3; Petersen & Hayward, 2007:i43; Rousounidis, 2011:3247; Van der Velden, 2013:319; Venmans *et al.*, 2009:e348-349). In addition to a literature search, discussions were conducted with local authorities in the field to get their understanding on what the focus of the questions in relation to Namibia should be.

Once the questions were identified, the next phase was to design the lay-out of the questionnaire. Once again, literature was used to see how other researchers constructed their questionnaire. Factors discussed under phase 3 of ensuring that the questionnaire is not too long, easy to read, clear on what is expected of the respondent and unambiguous were considered and employed. The length of the questionnaire was particularly important as self-administered surveys, though easy to carry out, are well known for low response rates.

The questionnaire had three sections – characteristics of respondents (general demographic information), current practice in prescribing antibiotics and general questions about antibiotic use and resistance in Namibia.

The questionnaire consisted mainly of close-ended questions and a few open-ended questions. The open-ended questions were more related to practice – choice of antibiotics in given scenarios and thoughts on how to improve prudent use of antibiotics in Namibia.

The questionnaire was then submitted to medical professionals for review. These included infectious disease specialists, a microbiologist, an internal medicine physician and general practitioners.

With input from specialists, the questionnaire was updated and the second draft finalised for piloting. The questionnaire was then piloted by doctors in South Africa. The purpose of the pilot was to determine if the questions were clear, understandable and easy to complete.

The final questionnaire was then inputted into Survey Monkey® to design a web-based questionnaire. Survey Monkey is a cloud-based online survey platform and questionnaire tool that helps gather survey related information. It allows for real time data collection. It is easy to complete for the respondents and because it is completed online, it provided the assurances of anonymity (confidentiality) and the survey is received once the “submit” button is clicked (thus providing quick turn-around of completed surveys). It is a widely accepted and used survey tool – it is recognized as one of the top online survey tools for research. It generates frequencies of results and

allows for exporting to statistical tools for analysis. (Rhada & Trivedi, 2015:22; SurveyMonkey).

The web-based questionnaire was also tested by six medical professionals and one information technology specialist. The purpose of the information technology specialist was to make sure that the questionnaire will produce the desired results, for example, that only one selection could be made for dichotomous questions and that prompts used (for example, specifying specialty of specialist box) were active and easy to complete. The reported average time for completing the questionnaire was 8 minutes.

1.7.4.5. Reliability and validity

Concepts of reliability and validity and factors affecting these for questionnaires were discussed in details under phase 3 of this study. This section will therefore only highlight what was done with the questionnaires to ensure reliability and validity.

As with the previous questionnaire, works of other researchers as well as specialists in the field were used in the design of the questions. Furthermore, the questionnaire was piloted to ensure that it was clear and unambiguous, measured the construct it was intended to measure and that it was comparable to other questionnaires used in the field.

The questionnaire was sent to all medical professionals belonging to the two associations in Namibia. While not all doctors belong to any of these associations, the associations cover the majority (70%) of the doctors practising in Namibia and should therefore make generalization possible.

The data on the questionnaires were entered directly into the Survey Monkey® database when the respondents submitted the questionnaire. The data therefore was not and could not be manipulated by the researchers.

1.7.4.6. Questionnaire administration

As already alluded to in the preceding sub-sections, the questionnaire that was finally submitted to the doctors was web-based. Requests were sent to the two medical associations operating in Namibia to support the study by facilitating the distribution of

the questionnaire to their members. Electronic mails, followed by telephone calls and finally formal letters were used for the request (a copy of the letter is in annexure E).

A brief description of the study was then sent together with the link to the survey to the medical associations. The description indicated the purpose of the study, the fact that it was anonymous and that it was completely voluntary. The medical associations sent the link to their members. The medical associations were sent reminders twice during the data collection period.

After 6 weeks of data collection and two reminders to the associations, the response rate was very low. The methodology was then adapted to convenient sampling to increase the response rate. The telephone directory was used and doctors in Windhoek were called and asked if they would participate in the survey. The response was by and large negative. Doctors whom we knew were then contacted and asked to participate and to share the survey with their colleagues. A few more responses were collected in this way. Finally, questionnaires disseminated during various Continuing Professional Development (CPD) sessions with doctors and doctors were requested for participation in the survey. A few more responses were collected using this method.

Data were collected between 01 March and 31 July 2014.

1.7.4.7. Data analysis

Study variables (independent) that were identified for analysis for this phase included:

- Age;
- Gender;
- Type of provider (general practitioner or specialist) and specialty;
- Region of practice;
- Sector of practice (public or private sector);
- Length of practice;
- Patient load;
- Association with a medical association; and
- Availability of treatment guidelines.

Other variables related directly to practice/behaviour and perception were also analysed. These are when are antibiotics prescribed and which antibiotics are prescribed in specific infection conditions; and whether patients are evaluated for adherence and how often.

Because the questionnaire was web-based, the responses were entered directly into the database by the respondents. Therefore, the researcher did not have to make any data entries. Data were then exported from Survey Monkey® to Excel® where they were checked for completeness. Data were then exported to SAS Version 9.1.3 (SAS Institute, Cary, NC) for analysis.

Detailed discussion of statistical analysis is discussed under section 1.8.

1.7.4.8. Ethical considerations

Ethical clearance for this study was obtained from the North-West University Research Ethics Committee, Faculty of Health Sciences, North-West University (Ethical clearance number NWU-00028-13-s1). Additionally, permission was obtained from the medical associations to distribute the survey to respondents.

The study was anonymous to ensure confidentiality. Respondents were requested to participate and were informed of the voluntary nature of the study and those willing to participate completed the survey.

1.8. Statistical analysis

This section applies to all phases of the study.

For all sections, data were cleaned and manipulated in Excel®, as described under each section. These data were then exported to SAS version 9.1.3 (SAS Institute, Cary, NC) for analysis. Additionally, for phase 2 of the study, Statistical Package for the Social Sciences **(**SPSS®) version 12.0.1 (IBM SPSS, NY, USA) was used.

Both descriptive and inferential statistics were used to analyse and report the data.

1.8.1. Descriptive statistics

Descriptive statistics are ways of summarising large amounts of data to provide an overall concise and coherent picture (Katzenellenbogen *et al.*, 2004:108). Because the data in this study were either categorical or numerical, descriptive statistics of frequencies and measures of distribution (location and spread) were used.

a. Frequencies

Frequencies refer to the number of times a result occurs and they are obtained by simply counting occurrences of the variable of interest presented in the data. These data can be presented either in numbers or percentages or both. In this study, both numbers and percentages were used to report data (Utts & Heckard, 2007:20).

b. Location

Location is measured by mean, median and the spread.

- *Arithmetic mean* refers to the numeric average calculated as the sum of data values divided by the number of the value (Utts & Heckard, 2007:37). It is represented by the formula below:

$$\bar{x} = \frac{\sum xi}{n}$$

Where:

$\bar{x}$= average

$\sum xi$ = sum of all given x values

n = number of observations in the sample

- *Median* – this refers to the middle data value after the data has been organised in order from lowest to highest (Maree, 2010:187).

c. Spread

Spread refers to the variability among different values and its measures include range, standard deviation and variance.

- *Range*-Range is the difference between the highest and lowest values (Katzenellenbogen, 2004:111). It is used in all four phases of the study.
- *Interquartile range* is the range of the middle 50% of the data (Utts & Heckard, 2007:4146). In this study, percentiles were used (which are a form of quartiles). K^{th} percentile simply means that *k* percentage of the data values are on or below the *k* value and 100 – *k*% are above the *k*-value (Utts & Heckard, 2007:46). In this study, this was used in classification of patients and respondents by age groups in phases 1, 3 and 4.
- *Standard deviation*-This is the unit that measures deviation of each score from the mean (Anderson *et al.,* 2009:95; Struwig & Stead, 2001:158). In this study, the standard deviation was used in the analysis of age of patients who received antibiotics, cost of antibiotics and fluctuations in antibiotic usage. In phases 3 and 4 it was used in the analysis of the age of respondents.

d. Confidence Interval (CI)

Throughout the study, 95% confidence interval was used. Confidence interval is the range on either side of the estimate that is likely to contain the true value (Struwig & Stead, 2007:113).

1.8.2. Inferential Statistics

Data management and analysis was performed in SAS Version 9.1.3 (SAS Institute, Cary, NC). For phase 2 of the study, the SPSS was used for analysis. All statistical significance was considered with probability of $p < 0.05$. The practical significance of the results was computed when the *p*-value was statistically significant ($p \leq 0.05$). Cross-tabulations were generated for different variables in each of the phases. The aim of the cross tabulations was to determine which variables seemed to be related.

The Chi-square ($\chi 2$) test is a test that is used to assess the statistical significance in the association between two variables (Maree, 2010:246; Utts & Heckard, 2007:635). It was used in all four phases of this study to determine if an association exists between proportions of two or more groups.

Following the Chi-square test, the Cramer's *V* statistics test was used to determine the practical significance of this association. While the Chi- square ($\chi 2$) says there is a significant relationship between two variables, the Cramer's *V* is a post-test that provides additional information regarding the effect of the association or the practical significance of the association (Utts & Heckard, 2007:208-216).

In phase 2 of the study, the analysis of the relationship between antibiotic usage and resistance was conducted. The Pearson correlation coefficient, which computes of the strength of the linear relationship between two quantitative variables, was used (Maree, 2010:234; Utts & Heckard, 2007:165; Wegner, 2007:418). However, because the data were not evenly distributed, Pearsons correlation was not the best choice of test. The Spearman correlation coefficient test was then used. This is also a measure of association between two variables but it is a non-parametric (distribution free) measure (Maree, 2010:237).

1.9. Division of chapters

This study is reported in four chapters which are presented as follows: Chapter 1, which gives an overview of antibiotic use and resistance globally and regionally as well as the research methodologies used in conducting this study. Chapter 2 provides in-depth discussions on concepts of antibiotics and resistance, impact of resistance globally and in Namibia, overview of the Namibia health system and regulatory management of antibiotics in Namibia. Chapter 3 presents results and discussions in the form of articles submitted (or prepared for submission) to journals. The final chapter presents the conclusion, recommendations and limitations drawn from this study.

1.10. Chapter summary

This chapter introduced the rationale for and objectives of the study on antibiotic usage in the private sector of Namibia. It also detailed the research methodology that was followed to achieve the objectives of the study.

Chapter 2: Literature Review

2.1. Introduction

Chapter 1 gave an overview of the objectives of the study and the research methodology followed in undertaking the study. This chapter lays the foundation by discussing the concepts of antibiotics and resistance and looking at the impact of antibiotic resistance globally and in Namibia. The chapter also sets the stage for the study by expounding on the Namibia health and regulatory system and how that can influence the appropriate use of antibiotics and the development of resistance.

2.2. Antibiotics and the development of resistance

The World Health Organization (WHO) hails the discovery of antimicrobials as one of the important advances in health in human history-decreasing suffering from disease and saving lives. Up until their discovery, the major cause of death for mankind was infectious diseases caused by organisms such as bacteria, viruses, fungi and parasites (WHO, 2012a).

Antibiotics are naturally occurring low molecular weight substances (made by living organisms) or synthetic (chemically altered) low molecular weight substances that selectively inhibit the growth or multiplication of bacteria or kill bacterial cells directly (Gillings, 2013:1; Powers *et al.*, 2010). These drugs typically impede bacterial production by entering the microbes and interfering with production of components needed to form new bacterial cells (Gillings, 2013:1; Levy, 1998:47).

Antibiotics inactivate bacteria through five basic mechanisms of actions (Aziz 2013: 1066; Chambers, 2006: 4; Ebrahim 2010:142; Kaufman 2011:51; Levy & Marshall, 2004:S124; Powers *et al.*, 2010). The table below summarises these actions with examples.

Table 2-1: Mechanism of action of antibiotics

Mechanism	Antibiotic class
Inhibition of cell wall synthesis	Beta-lactams,
Inhibition of protein synthesis	Aminoglycosides, tetracyclines, macrolides, lincosamides
Inhibition of DNA synthesis	Fluoroquinolones
Inhibition of RNA synthesis	Rifampin
Competitive inhibition of folic acid synthesis	Sulfonamides, trimethoprim

There are four different ways in which antibiotics are used (Ferguson, 2004:39-41; Paterson, 2006:4-5).

- First, antibiotics may be used prophylactically to prevent infection. The most common use is prior to surgery to minimise or prevent surgical wound infection. Wound infection is said to be the most common hospital-acquired infection among surgical patients (Munckhof, 2005:38). If used correctly, prophylactic administration of antibiotic reduces the growth of contaminating bacteria and in cases where prosthesis implants are used, the antibiotics reduce the adherence of bacteria to the prosthesis. In so doing, the antibiotic reduces the development of infection thus reducing length of stay in hospital and the costs associated with treating wound infections. Other examples of prophylactic use include in immunosuppressed patients (HIV/AIDS patients) to prevent the development of *Pneumocystis* pneumonia; and to prevent the transmission of a communicable pathogen. While prophylactic use of antibiotics reduces chances of infection (Leekha, 2011:164), the increased use of antibiotics prophylactically increases selective pressure favouring the development of resistance (SIGN, 2008:12).
- Second, antibiotics may be used as empiric treatment. This refers to the use of antibiotics directed at a particular syndrome without prior identification of the organisms causing the infection. Often microbiological results do not become

available for 24 to 72 hours and delays in initiating treatment could have dire consequences for the patient (Deresinki, 2007:S177). Immediate initial therapy for infection is therefore needed and is guided by the clinical presentation. When used appropriately, empirical antibiotic treatment results in better survival and shortened duration of hospital stay (Fraser *et al.*, 2006:973). On the other hand, inappropriate empiric treatment was associated with increased mortality among severely ill patients (Deresinki, 2007:S178). Fraser *et al.* (2006:972) also reported prolonged hospital stays associated with inappropriate empirical treatment.

- Third, antibiotic use may be pathogen-directed whereby the organism causing the infection is known but the susceptibility of the organism is unknown. This is similar to the empiric use of antibiotic in the sense that treatment is not based on microbiological susceptibility results. For this to be effective, an antibiotic with high degree of activity against the offending bacteria or an antibiotic with low resistance profile should be used. Furthermore, treatment choices should be based on local susceptibility profiles. The advantages and disadvantages are the same as those mentioned under empirical use above.
- Finally, antibiotic therapy may be susceptibility guided. In this case, both the identity of the organism causing infection and the susceptibility profile of the organism are known. Because the organism causing the infection and its susceptibility profile are known, appropriate therapy targeted at the organism can be selected. This is important to reduce the use of broad spectrum antibiotics in favour of narrow spectrum antibiotics which are “less likely to provoke the development of resistance” (Varley *et al.*, 2009:186-187). The main disadvantage of this is that as discussed above, microbiology results are often not immediately available and delaying treatment while waiting for results could have dire consequences (Deresinki, 2007:S177).

Whatever the reason for use, there are guiding principles that ensure that antibiotics are used appropriately so as to minimise inappropriate or overuse.

General principles of antibiotic prescribing include (Dipiro *et al.*, 2008:1731; Ferguson, 2004: 40- 41; Leekha *et al.,* 2011:158-159; Powers *et al.*, 2010; Varley *et al.*, 2009:86-87):

- Knowing the identity of the causative/infecting organism-this is important in ensuring that the most appropriate antibiotic for the specific organism is selected;

- Knowing the local susceptibility patterns-the antibiotic selected should have demonstrated effectiveness against the specific organism;

- Spectrum – broad-spectrum antibiotics are preferred for initial empiric therapy for critically ill patients. Narrow spectrum antibiotics are more generally preferred where possible, especially if prophylactic treatment is chosen;

- Dose – dose selected should achieve inhibitory concentrations;

- Duration – excessive duration of antibiotic therapy increases the risk of the development of resistance and predisposes the patient to unnecessary side effects.

- Consideration of patient factors (such as age, pregnancy, renal disease and adverse events) and cost. Patient convenience and cost are important considerations as they promote better adherence (Cunha, 2011:12; Powers *et al.,* 2010).

To ensure their continued efficacy, antibiotics should be used prudently by avoiding overuse and misuse and encouraging appropriate use. Antibiotics should only be used when they are known to have an effect and where indicated and only those that will limit the development of resistance should be selected (Dipiro *et al.*, 2008:1731; Ferguson, 2004:40).

2.2.1. Consequences of inappropriate use of antibiotics

The use of antibiotics has changed the face of modern-day medicine by making the management of infectious disease easier and contributing significantly to decreased morbidity and mortality due to infectious diseases (Alanis, 2005: 697; Chandy *et al.*, 2013:229; CDC, 2012:2; Finley *et al.*, 2013:1; Holloway *et al.*, 2011a:152; Rice, 2008: 1079). However, these gains which present day medicine is so used to, are threatened by the development of resistance to antimicrobials including antibiotics (Ashley *et al.*, 2011:1167; CDC, 2013:11; MacGowan, 2008:ii105; World Economic Forum 2013: 29). Infections and pathogens that could once be controlled by antibiotics are returning in new strains resistant to these antibiotics (Levy & Marshall, 2004:S122). Inappropriate use of antibiotics especially overuse has been cited to be the major contributor to the development of resistance (CDC, 2013:11; Knober *et al.,* 2003:19; WHO, 2011a; WHO 2012b:2). In their report on "the global need for effective antibiotics – moving towards concerted action", Cars *et al.* (2011:68), state that the extensive and inappropriate use of antibiotics has resulted in the global spread of antibiotic resistant bacteria.

The WHO declared antimicrobial resistance to be one of the top three issues in global health (Knobler *et al.*, 2003:20) and at the recent June 2013 G8 Science Minister's meeting, antimicrobial resistance was pronounced a major health security challenge (G8 meeting UK, 2013). The WHO (2012a) further described the concerns for the development of resistance among others as prolonged illness and greater risk of death due to resistant organisms failing to respond to standard treatment; reduced control of infectious disease as patients remain infected for longer due to reduced effectiveness of treatment and thus potentially spread resistant organism to others; and increased health care cost as resistance to standard first line therapies necessitates the use of more expensive therapies (WHO, 2012a; WHO 2012b: 3). In the statement for the World Health Day in 2011, the Director-General of the WHO expressed that with the rates of antimicrobial resistance the world is moving towards the post-antibiotic era in which common infections will no longer have a cure and therefore result in costs-both money and lives (WHO, 2011a). These sentiments are further echoed in the 2013 Global Risk Report of the World Economic Forum which recognises antimicrobial resistance as a

greatest risk to human health (World Economic Forum, 2013:29-32). The report states that bacterial mutations outpace new innovations and further suggests that new innovations may not be effective against some resistant mutations (World Economic Forum, 2013:29-32).

Antimicrobial resistance is the ability of microbes to grow in the presence of a medicine that would normally kill them or limit their growth (Aziz, 2013:1067; Hashemi *et al.*, 2013:384; NIAID, 2011; WHO 2014b). Microbes are constantly evolving, enabling them to adapt to changing environments. This “adaptation” of microbes to the environment occurs through changing of their genetic structure. Genetic changes that result in the development of resistance can either occur through natural causes (mutation and gene transfer) or societal pressure (Kaufman, 2011:52; Lancet Commission, 2013: 1; NIAID, 2011).

Several mechanisms have evolved in bacteria which confer them with antibiotic resistance. These mechanisms can chemically modify the antibiotic, render it inactive through preventing entry and/or physical removal from the cell, or modify the target site so that it is not recognised by the antibiotic. The mechanisms are summarised as follows (Aziz, 2013:1068; Ebrahim, 2010:141; Kaufman, 2011:53; Levy & Marshall, 2004:125; Levy, 1998:48, Levy, 2002:27; Mulvey & Simor, 2009:409-411; Raghunath, 2008:595; Tenover, 2006: S4-S5):

- *Inactivating antibiotics* - the organism may acquire genes encoding enzymes, such as β-lactamases, that destroy the antibacterial agent before it can have an effect. B-lactamases produced by many staphylococci inactivate most penicillins and extended-spectrum β-lactamases inactivate third and fourth generation cephalosporins. Some enzymes chemically alter the antibiotic making it inactive e.g. aminoglycoside modifying enzymes, acetylases for chloramphenicols and esterases for macrolides.
- *Impaired uptake of antibiotic*. Bacteria may acquire efflux pumps that extrude the antibacterial agent from the cell before it can reach its target site and exert its effect, that is, mutations in the genes encoding the outer membrane proteins

(porins) involved in transport of amino acids as well as antimicrobials alter sensitivity to antibiotics especially when there is synergy between the permeability barrier and multidrug efflux pumps. Tetracycline resistance is an example of this mechanism.

- *Alteration of binding sites*. Aminoglycosides, for example, bind to bacterial ribosomes and inhibit protein synthesis. In resistant organisms, the binding sites may be altered so that they no longer have affinity for the drugs.

- *Development of alternative metabolic pathways*. This allows the bacteria to grow in the presence of the antibiotic.

Once bacteria have developed resistance to the antibiotic, the resistant gene can be spread from one bacterium to another through various mechanisms which can either be vertical or horizontal. Vertical transfer is when the resistant genes are transferred directly to all the bacteria's breed (new generation) during DNA replication (APUA; Dutta & Pan, 2002:27; Lawrence, 2005:255; Todar, 2012). The process is driven by principles of natural selection: a spontaneous mutation in the bacterial chromosome imparts resistance to a member of the bacterial population. In the selective environment of the antibiotic, the wild types (non-mutants) are killed and the resistant mutant is allowed to grow and flourish (Todar, 2012).

Horizontal or lateral gene transfer is a process whereby resistant genes can be transferred between individual bacteria within or across species (APUA; Dutta & Pan, 2002:27; Gillings, 2013:2; Lawrence, 2005: 255; Raghunath, 2008:595). Within the genome environment there is resistome, a collection of genes that potentially encode resistance. The resistome interfaces with the mobilome – the mobile genetic elements in the genome. These elements specialise in transporting DNA within and between genomes. These include plasmids, transposons, integrons, insertion sequence and integrative conjugative elements (Gillings, 2013:3). Horizontally acquired resistance genes are thus carried on these plasmids and are transferred from one cell to another by mating or conjugation. Some antibiotic resistance genes are held within transposons

or integrons (mobilome). These elements in addition to capturing and organising the expression of resistance genes, are also capable of moving from plasmids to the chromosome, a feature that stabilises their inheritance (Okeke & Sosa, 2008:4).

Mechanisms of horizontal gene exchange are transduction, transformation or conjugation. For each of these processes, transposons may facilitate the transfer and incorporation of the acquired resistant gene into the host's genome or into plasmids. (Todar, 2012; Tenover, 2006:S5).

Conjugation occurs when there is direct cell-cell contact between two bacteria (which need not be closely related) and transfer of small pieces of DNA called plasmids takes place. Plasmids can move genes between bacteria of different evolutionary backgrounds including transfer between gram-positive and gram-negative bacteria. (Todar, 2012; Levy, 2002:26).

Transformation is transfer of chromosomal genes between bacteria through the uptake by one bacterium of naked DNA released by another bacterium into the environment after cell lysis. This is a mechanism documented in the emergence of resistance among pneumococci and *Haemophilus influenza* species. (Levy & Marshall, 2004:S124; Tenover, 2006:S5).

Transduction occurs when bacteria-specific viruses (bacteriophages) transfer DNA between two closely related bacteria. (Todar, 2012; Tenover, 2006:S5; Levy, 1998:49; Levy, 2002: 26).

2.2.2. Antimicrobial resistance: The extent of the problem

The development of antimicrobial resistance is a growing concern worldwide. Data from around the world supports the notion that antimicrobial resistance among pathogens commonly found in both hospital and community settings is on the rise (WHO, 2012b:3). This increase in resistance which is seen among both gram-positive and gram-negative pathogens has been cited by others as a global public health crisis due to the threat it poses on both morbidity and mortality (Spellberg *et al.*, 2008:155; Bartlett, 2011:S4).

Resistance renders the tools that the health professionals have in treating infectious disease ineffective thus impacting negatively on patient outcomes (CDC, 2010:1-2; Kimang'a, 2012:136; Nyasulu *et al.*, 2012:8).

In their publication "Antibiotic resistance threats in the United States" in 2013, CDC reported that two million people are sick and a further 230 000 people die yearly due to antimicrobial resistance (CDC 2013:11). In 2009, the European community reported at least 25 000 people dying yearly due to infections with resistant bacteria (Freire-Moran *et al.*, 2011:119). While there is scarcity of accurate and reliable data on the impact of antibiotic resistance in the developing countries, the high burden of infectious diseases and limited resources in these countries would suggest an even higher impact (Laxminarayan & Heymann, 2012:1; The Lancet Infectious Diseases Commission, 2013: 3)

Resistance has been reported in many pathogens in all regions including in developing countries, and has been seen among many of the major bacterial pathogens (Byarugaba, 2005:617, 623; Howard *et al.*, 2003:S6). In 2008, Rice (2008:1079) reported a group of six gram-negative and gram-positive bacteria that have emerged that are "capable of escaping the effects of antibiotics". These bacteria are termed "ESKAPE' both to identify them as well as to emphasise their ability to escape the lethal action of antibiotics. These pathogens are *Enterococcus faecium, Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa,* and *Enterobacter* species. According the United States Centres for Disease and Control, these pathogens are responsible for two thirds of all health care-associated infections in that country. In 2011, John Bartlett (2011:S4) suggested that *Clostridium difficile* be added to the list. In the letter to the Food and Drug Administration (FDA), the Infectious Diseases Society of America (IDSA) added to the ESKAPE list *Clostridium difficile, Mycobacterium tuberculosis* and *Neisseria gonorrhoeae* (IDSA).

These pathogens are not only a challenge in the US. Huttner *et al. (2013:2-3)* report the same pathogens in their paper on global view of antimicrobial resistance. The same list, with the addition of *Shigella spp* and *Salmonella spp* was earlier reported in China and

Kuwait (Zhang *et al.*, 2005: 13). In 2009, high levels of *Staphylococcus aureus* were reported in eight European countries and Taiwan (Nelson *et al.*, 2009:6).

Developing countries have also seen similar patterns of resistance to important pathogens (Lancet Infectious Diseases Commission, 2013:2; Vlieghe *et al.*, 2009:1). For example, Pakistan reported high levels of resistance to *Acinetobacter baumannii, Klebsiella pneumonia, Staphylococcus aureus* and *Escherichia coli* (Perry *et al.*, 2011:2291–2292; Saleem *et al.*, 2013: e964; Saleem *et al.*, 2010:32). Resistance to the same pathogens has been reported also in India (Holloway *et al.*, 2011a: 370; Nagaraj *et al.,* 2012; Nordmann *et al.*, 2009: 233; Shahid *et al.*, 2008:263). Other countries such as China and South America have also reported increased resistance to similar pathogens (Nordmann *et al.*, 2009: 233).

Africa is no exception to this scourge of resistance. Trends of resistance to pathogens such as *Staphylococcus aureus, Neisseria gonorrhea, Klebsiella pneumonia, Streptococcus pneumoniae, Escherichia coli, Pseudomonas aeruginosa and Shigella* spp. were reported all across Africa (Kimang'a, 2012:136-137).

Some examples include:

a) *Staphylococcus aureus*

Bustamante (2011:7) reported prevalence rates of methicillin resistant *staphylococcus aureus* (MRSA) in Africa ranging from 5% in Madagascar to 45% in Algeria (South Africa reporting 40%). The same study showed antibiotic resistance patterns ranging from 11% for gentamycin (Madagascar) to 88% for erythromycin, cotrimoxazole and chloramphenicol (in Uganda) (Bustamante, 2011:12). In the same year, Ashley and colleagues reported high degree of resistant *Staphylococcus aureus* in Sub-Sahara Africa (Ashley *et al.*, 2011: 1170). In 2014, similar findings to those reported by Busmante were reported by Falagas *et al.* (2013: 6, 8). They reported prevalence of MRSA in Africa ranging from 6% in Madagascar to 52% in Egypt. In 2012, Nyasulu *et al.* (2012: 11) reported MRSA resistant rate of 33% in South Africa. Falagas *et al.* (2014:6) reported in 2014 that MRSA prevalence in South Africa decreased to 24%.

Huson and colleagues (2014:454) reported resistance rates of 11% in Gabon and 28% in Cameroon.

Studies conducted in South Africa showed that up to 80% of MRSA were resistant to at least four classes of antibiotics (Heysell *et al.*, 2011:333; Marias *et al.*, 2009:172). Similar patterns of resistance were reported in Kenya (Aiken *et al.*, 2014: 4), Uganda (Ojulong *et al.*, 2008: web page) and Nigeria and Cameroon (Vlieghe *et al.*, 2009:2; Udobi *et al.,* 2013: 3). A study conducted in 2013 in Namibia revealed high levels of *Staphylococcus aureus* resistance (78%) to most antibiotics (Mengistu *et al.*, 2013: 3).

b) Klebsiella pneumoniae

Studies have shown that susceptibility of *Enterobacteriaceae* in Africa is comparable to the rest of the world (Tansarli *et al.*, 2013:3637). For instance, Ashley *et al.* (2011:1173) reported high rates of resistance to *Klebsiella* to common antibiotics across Africa. In Central Africa, Vlieghe *et al.* high rates of resistance, especially to amoxicillin and clavulanic acid and emerging resistance to third generation cephalosporins. This however is different to what was earlier reported by Bercion *et al.* who found increasing resistance of *Klebsiella* pneumonia to third generation cephalosporins in Bengui, Central African Republic (Bercion *et al.*, 2009: 189). Ahmed and colleagues (Ahmed *et al.*, 2013:281) reported very high rates of resistance of *Klebsiellapneumoniae* to cephalosporins and macrolides in Nigeria, and isolates of multidrug resistant *Klebsiellapneumoniae* in Egypt. In Southern Africa, studies carried out in Madagascar, Namibia and South Africa also showed similar reports of high resistance rates of *Klebsilla pneumoniae* to multiple antibiotics (Mengistu *et al.,* 2013:4; Nyasulu *et al.,* 2012:11; Randrianiria *et al.*, 2010:76).

c) Escherichia coli

In their review of the literature, Ashley *et al.* (2011) found numerous studies that reported high levels of resistance of *E. coli*, a leading pathogen causing urinary tract infections and other infections, to numerous first line antibiotics including amoxicillin/ampicillin, chloramphenicol, cotrimoxazole (Ashley *et al.,* 2011:1173). This

supports what was reported by Okeke *et al.* (2007:1641) that resistance of *Escherichia coli* to almost all drugs is high and continues to rise in most African countries including Gabon, Ghana, Kenya, Nigeria, Tanzania and Zimbabwe. In Ethiopia, the study conducted by Kibret and Abera (2011:S43) found high levels of resistance of *E. coli* to commonly used antibiotics including tetracycline, amoxicillin and erythromycin. Still in East Africa, Muvunyi and colleagues reported similar multi-drug resistant *Escherichia coli* in Rwanda (Muvunyi *et al.*, 2011:926). Similar resistance of *Escherichia coli* to multiple classes of antibiotics was noted and reported in West Africa, Nigeria (Mehta *et al.*, 2012: L9- L10; Raji *et al.*, 2013: 433) and Rwanda. Central Africa also reported very high resistance rates to commonly used antibiotics with the Democratic Republic of Congo, Gabon and Central African Republic reporting multi-drug resistant *Escherichia coli* (Bercion *et al.*, 2009: 188–189; Vlieghe *et al.,* 2009:5). In Southern Africa, Madagascar reported high level of ciprofloxacin resistant *Escherechia coli* while Namibia and South Africa both reported multi-drug resistance (Kinge *et al.*, 2010: 48; Mengistu *et al.*, 2013: 4; Randrianiriai *et al.*, 2010:79).

All these authors concluded that these results were similar to studies conducted in other parts of Africa and the world.

d) Neisseria gonorrhoeae

Studies conducted in Africa report that *Neisseria gonorrhoeae* isolates resistant to penicillin range between 15% and 82% whereas the prevalence of tetracycline-resistant *Neisseria gonorrhoeae* varies from 20% to 65% (Apalata, 2009:341).

Studies conducted in South Africa over a 5-year and 20-year period in Durban and Pretoria, respectively, showed increasing resistance to quinolones, tetracyclines and penicillins (Moodley *et al.*, 2001:855; Dangor *et al.*, 2010:12) by the pathogen *Neisseria gonorrhoeae*. In Malawi, high resistance of *Neisseria gonorrhoeae* to penicillin and tetracycline were observed (Brown *et al.*, 2010:121). A cross-sectional study conducted in Maputo, Mozambique, also showed high levels of resistance of *Neisseria gonorrhoeae* to penicillin and tetracycline, specifically 65% for penicillin and 77% for

tetracycline in 2005 (Apalata, 2009:342). In other parts of Africa, penicillin resistance in *Neisseriagonorrhoeae* was reported in Cameroon (60%), Rwanda (70%), Madagascar (81%), Nigeria (95%), Central African Republic (80%) and Ethiopia (85%) (Cao *et al.*, 2008:942-943).

e) Shigella spp. and *Salmonella spp*.

Africa, like the rest of the developing world has a high incidence of diarrhoeal diseases occurring annually (Yilgwan & Okolo, 2014: web page).

Shigella spp and *Salmonella spp* are listed among the common causes of diarrhoeal diseases together with *Escherichia coli* (World Gastroenterology Organisation, 2012: 3–4). Antimicrobial drug resistance is a large and growing problem among organisms that cause these diarrhoeal diseases (Obi *et al.*, 2003:589; Okeke *et al.*, 2007:1641). In a study conducted in rural Mozambique, 65% of *Shigella* isolates and 23% of *Salmonella* were reported to be multi-drug resistant to first line treatment (Mandomando *et al.*, 2009:2452-2453). Similarly, high levels of resistance to commonly used first line drugs by both *Shigella* and *Salmonella* were reported by Reda *et al.* (2011:136) in Ethiopia. The same authors concluded that these levels were consistent with those reported in studies conducted in Kenya and Eritrea (Reda *et al.,* 2011:136). Vlieghe *et al.* (2009:4) also reported high levels of multi-drug resistance in the Democratic Republic of Congo (DRC) and Central African Republic (CAR). South Africa is no exception. Multi-drug resistance to at least four antibiotics used as first line treatment was reported by GARP in 2011 and by the National Institute for Communicable Diseases in 2013 (Crowther-Gibson:2011; National Institute for Communicable Diseases, 2013:12,16).

Resistance is occurring at a fast pace (Nelson *et al.*, 2009:5).This echoes what was reported by Levy a decade ago (2003:34-35) in his write up on "*Antimicrobial resistance, a decade journey"*.

Complicating the matter is that while resistance to available antimicrobials is on the rise, the development of newer antimicrobials is slower due to lack of economic incentives and increasing development costs (Carlet *et al.*, 2011:370; WHO, 2001:12; WHO,

2011a; Simonsen *et al.*, 2004: 929). This could lead to a situation where health care professionals will not have appropriate medications to effectively treat all patients who develop infections (Bartlett, 2011:S5; Boucher *et al.,* 2009:7; Freire-Moran *et al.*, 2011:122; Han & Ramsay, 2013: 368; Pendleton *et al.*, 2013:297). This dearth of new antibiotics in the pipeline indicates the urgent need to conserve the efficacy of available antibiotics to avoid reverting back to the post-antibiotic era.

Drug-resistant strains of bacteria are prevalent in both hospital and community settings and as already mentioned above, they cause increased avoidable health costs and unnecessary disability and death

2.2.3. Antibiotic resistance in hospitals settings

Problems associated with antibiotic resistance are typically magnified in hospital settings. Hospital settings provide a fertile ground for the spread of resistant microbes (Levin & Andreasen,1999:800). According to Struelens (1998:652), this is the consequence of exposure to heavy antibiotic use, a high density patient population in frequent contact with healthcare staff and the attendant risk of cross infection.

Hospital-acquired infections often involve transmission from patients who carry the bacteria asymptomatically to other patients, some of whom then may become infected with the colonising strain (Lipsitch, 1999:1938). According to Nicolle (2003:139), large hospitals providing tertiary care and teaching hospitals have a higher prevalence of resistance than smaller community hospitals and have repeatedly been the site where new resistance is first described.

Hospitals worldwide are faced with the emergence and spread of antibiotic resistant organisms. According to Levy and Marshall (2004:S122-123), 40–60% of nosocomial *Staphylococcus aureus* strains in USA and UK are methicillin-resistant (MRSA) which is associated with more deaths than with methicillin-sensitive strains. They further indicate that other bacteria resistant to multiple antibiotics among hospital patients include *Pseudomonas aeruginosa*, *Acinetobacter baumanii*, *Enterobacter spp.* and *Klebsiella spp*. Similarly, Mulvey and Simor (2009:409) reported the same organisms as well as

Clostridium dificale to be antimicrobial resistant organisms among patients in Canadian hospitals in 2008. In Singapore, a national antimicrobial resistance surveillance program in Singapore public hospitals detected high levels of methicillin resistance among *Staphylococcus aureus* (35.3%), carbapenem resistance among *Acinetobacter* spp. (49.6%), and third-generation cephalosporin resistance among *Klebsiella pneumoniae* (35.9%) hospital isolates in 2006. (Hsu *et al.*, 2007:1945).

Mir and Zaidi (2010:348) assert that agents causing nosocomial infections in the developing world hospitals more or less follow the trends seen in the developed world. For example, countries such as South Africa, Kenya, Uganda, and Ethiopia have reported MRSA as already discussed above. A study conducted in Antananarivo, Madagascar, showed high resistance to multiple antibiotics by *Enterobacteriaceae*, *Escherechia coli*, *Acinetobacter baumanii* and *Pseudomonas aeruginosa* (Randrianirina *et al.,* 2010:76). A systemic review of published literature on antimicrobial resistance among nosocomial pathogens in South Africa reported resistance by *Staphylococcus aureus, Klebsiella pneumoniae* and *Pseudomonas aeruginosa* (Nyasulu, 2012:9)

Risk factors associated with spread of antibiotic resistance in hospitals include prior antimicrobial exposure, prolonged stay in hospital, patient overcrowding, inadequate isolation facilities and inadequate infection control (hand washing and equipment cleaning) and invasive devices (Mir & Zaidi, 2010:348-349; Kollef, 2000: 31; Byarugaba, 2004:108).

2.2.4. Antibiotic resistance in community settings

Initially, antibiotic resistance due to risk factors highlighted above occurred mainly in hospital and health care settings. However, recently trends of antimicrobial resistance within the community are being observed (Furuya & Lowly, 2006:36) and rising, such that the community has become equally plagued by multi-drug resistant organisms (Levy & Marshall, 2004:S123; Hillier *et al.*, 2002:241). According to CDC (2003:11), data shows that most antibiotic resistant infections occur in the community.

Some of the organisms seen to be multi-drug resistant in hospital settings such as *Staphylococcus aureus, Enterobacteriaceae* and *Escherechia coli* are also seen to exhibit similar trends within the community. The interim results of the ECO SENS project, an international survey conducted to investigate the prevalence and susceptibility of pathogens causing acute uncomplicated community-acquired urinary tract infections (UTIs) in primary care in the years 1999 and 2000, showed resistance of some strains of *Escherechia coli* to some of the first line drugs used to treat UTI (Hilliers *et al.*, 2002:245). Levy and Marshall (2004:123) also report similar findings.

Community acquired MRSA (CA-MRSA) are infections that occur in otherwise healthy people who have not been recently hospitalised nor had a medical procedure (Furuya & Lowly, 2006:41). CA-MRSA strains are different to those seen in hospitals and display enhanced virulence, spread more rapidly and cause more severe illness than traditional HA-MRSA infections, and can affect vital organs leading to widespread infection (sepsis), toxic shock syndrome and pneumonia (Todar 2012; Levy & Marshall 2004:S123).

Other organisms that exhibit multiple drug resistance to antibiotics include *Mycobacterium tuberculosis*, *Streptococcus pneumoniae, Streptococcus pyogenes, Neisseria Meningitides, Salmonella spp. and Campylobacter spp.* (Goossens & Sprenger, 1998:654; Furaya & Lowly, 2006:37; Levy & Marshall, 2004:S123).

Risk factors associated with the development and increasing trend of antimicrobial resistance in the community include increased volume of antibiotics to which communities are exposed (Byarugaba, 2004:106). It has been cited that the development of antibiotic resistance is directly linked to the use of antibiotics (Kimang'a, 2012:136). Furaya and Lowly (2005:36) reported that approximately 1.3 million kilogrammes of antibiotics were used in humans annually and most of these in outpatient settings. Many African countries have a high burden of community-acquired infectious diseases which dictate high volume of antibiotic usage (Okeke & Sosa, 2008:12). Other factors have been cited as inappropriate prescribing, self-medication, sharing of antibiotics by patients, misinformation and poor compliance. In developing

countries, other compounding factors are poverty and overcrowding (Goossens & Sprenger, 1998:656; Byarugaba, 2004:107; Furaya & Lowly 2005:36).

2.2.5. Economic impact

In addition to the negative clinical impact, resistance has on the outcomes of therapy, it also puts an economic strain on both the health system and the individual (Cars *et al.*, 2011:68; French, 2010:S5; Lancet Infectious Diseases Commission, 2013:3; Pendleton *et al.*, 2013:1). In 2013, the CDC estimated the cost on the US economy due to antibiotic resistance to be in excess of US$20 billion (CDC, 2013:11). This increase in health care cost is associated with higher morbidity (prolonged illness, hospital stay and complications) and increased medicine costs (CDC, 2013:11, Mulvey & Simor, 2009:413). Limited treatment options caused by resistance may often result in the need for more expensive and potentially more toxic drugs (Cars *et al.*, 2011:68; CDC, 2010:3; Chandy, 2008:174; Laxminarayan & Heymann, 2010:2).

The cost of treating resistant pathogens is considerably greater than that of treating susceptible strains (WHO, 2010a:27; WHO, 2014:37). For instance, Stone (2009: 418) shows that the cost of treating MRSA was US$4 000 more per infection compared to treating the susceptible strain of *Staphylococcus aureus*. In the same vein, the CDC reported the direct cost associated with treating tuberculosis (TB) in the US to be US$17 000 for the susceptible strain and US$430 000 for extremely drug resistant TB (XDR-TB) (Marks *et al.*, 2014:817). Welte *et al.* (2010) found that community acquired pneumonia was associated with high rates of hospitalisation and length of hospital stay. The review showed that the clinical and economic burden of community acquired pneumonia (CAP) in Europe is high.

Similar trends are seen in developing countries. A study found the cost of treating resistant TB to be US$1 838, US$2 342, US$3 125 in Ethiopia, Indonesia and Kazakhstan, respectively (Tiermesma *et al.*, 2014:5). These figures are considerably higher than those reported for treating susceptible TB US$260, US$169, US$929 in the same countries respectively (Tiermesma *et al.*, 2014:5). In South Africa, Pooran and

colleagues reported that treating drug-resistant TB cost up to 103 times more than treating drug-sensitive TB (Pooran *et al.*, 2013:8).

Other costs associated with resistance are cost not easily recognised or accounted for and therefore often forgotten (Hawkey, 2008: i2). These costs include socio-economic costs such as loss of quality of life and loss of productivity due to illness. As an example of the impact of these costs, the CDC estimates such indirect costs for resistant TB to be between US$124 000 and US$126 000 per case (CDC: website). Roberts *et al.* (2009:1181) reported the societal costs due to resistance in the United States to be between US$10.7 and US$15 million while the European CDC estimated these costs to be 1.5 billion Euros per year (ECDC, 2009:13). The World Economic Forum Global Risk report reported the societal cost associated with antibiotic resistance in Thailand to be US$2 billion per year (World Economic Forum, 2013:30).

2.2.6. Antibiotic stewardship: towards addressing the problem

With escalating trends of antimicrobial resistance and challenges related with it, there is a need to reverse the trend. Han and Ramsay (2013:368) suggest that the answer to reversing the trends and conserving available antimicrobials lies with antimicrobial stewardship. The Infectious Disease Society of America (IDSA) defines antimicrobial stewardship as "*the coordinated interventions designed to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial drug regimen, dose, duration of therapy, and route of administration*" (IDSA). The Association for Professionals in Infection Control and Epidemiology (APIC) gives a similar definition "*antimicrobial stewardship is a coordinated program that promotes the appropriate use of antimicrobials (including antibiotics), improves patient outcomes, reduces microbial resistance, and decreases the spread of infections caused by multidrug-resistant organisms*".

Stewardship seeks to achieve optimal clinical outcomes related to antimicrobial use (preserving the effectiveness of antimicrobial drugs), minimise toxicity and other adverse events, reduce the costs of health care associated with infections, and limit the selection for antimicrobial resistant strains (contain antimicrobial resistance) (IDSA).

Efforts to reduce antimicrobial resistance are a major point of focus by the World Health Organization and countries alike. In 2001, the World Health Organization (WHO) launched the first global strategy to counter the threat posed by antimicrobial resistance. As already highlighted that risk factors associated with the development of resistance are patient, provider, health facility and environment related; the strategy aims to implement interventions in all these areas. It targets five domains namely (WHO, 2012b:8-10):

- *Surveillance of antimicrobial resistance and use* – This entails collecting, analysing and reporting information on both antibiotic usage and antimicrobial resistance patterns. Routine antimicrobial susceptibility surveillance can detect the emergence of resistant pathogens and allow for prompt intervention. It is also essential in providing magnitude and trends on use patterns and where interventions are implemented, monitoring the effectiveness of these interventions. Furthermore, surveillance forms the basis for rational use by informing policies and guidelines (Masterton, 2008:S21; Essack, 2006:51b; Pflomm, 2002:S14);
- *Antimicrobial regulation* – regulation is important to ensure that antimicrobials used in the country are of good standard and that their sale is limited to minimise inappropriate use and overuse. Simonsens *et al.* (2004:931) suggest that in order for strategies for the containment of antimicrobial resistance to succeed, regulatory framework must be in place and functional.
- *Rational antimicrobial use* – Since resistance is attributed to selective pressure which is related to overuse and inappropriate use of antimicrobials, rational and appropriate use of antimicrobials may help reduce the selective pressure that promotes the emergence of resistance (Pflomm, 2002:13; Essack, 2006: 51b).
- *Antimicrobial uses in animal husbandry* – In addition to being used in humans, antibiotics are widely used in animal husbandry mainly to promote growth. It is estimated that 40% of all produced antimicrobials in the United States are used for the growth and development of animals. Limiting antimicrobial use for the

promotion of growth in animals may also decrease the potential for transmission of resistant micro

- organisms to humans through the food supply (Pflomm, 2002:S14; Simonsens, 2004:929);
- *Infection prevention and control* – inadequate infection control practices and sanitation can fuel the spread of infections and resistance both inside and outside of the hospital settings (Okeke *et al.,* 2005:569; Essack, 2006:51c). Therefore, instituting various infection control measures can reduce the transmission of infection with resistant antimicrobials (Simonsens, 2004:930; Pflomm, 2002:S15);
- *Fostering innovations* – with the decline in the development of new antimicrobial agents, there is a need for innovative thinking to facilitate the minimization of the spread of resistance. Innovative thinking is needed in all the areas mentioned above as well as in areas of research, funding and new technologies.

Table 2-2 provides a summary of the interventions recommended by the strategy which includes hospitals, community and the government.

Table 2-2: Summary of WHO-recommended interventions to contain antimicrobial resistance

Target Group	Recommended Interventions
Patients and general community	Education to promote appropriate use and discourage self-medication
	Education on infection control measures such as vaccination
	Education on measures to reduce disease transmission such as hygiene
Prescribers and dispensers	Education on appropriate use
	Education on disease control and infection control
	Monitoring and supervision
	Professional regulation
	Development and use of guidelines and formularies
Hospitals	Establishment of infection control programmes (including hand washing, barrier precautions and patient isolation) and committees
	Establishment of therapeutic committees
	Development of antimicrobial guidelines
	Antimicrobial use surveillance
	Antimicrobial resistance surveillance through laboratory networks
Food producing animals	Development of guidelines for antimicrobials in veterinary use
	Surveillance of use and resistance
	Banning or phasing out of growth promoters
	Regulation of antimicrobial use in animals
Governments and health systems	Commitment to a national AMR task force with a budget
	Development of national drug policies (essential drug list and standard treatment guidelines
	Registration and regulation of dispensing outlets and antimicrobials
	Quality assurance for antimicrobials
	Continuing education on resistance and STGs
	Ensuring evidenced-based drug information and monitoring drug promotion
	Monitoring and linking of resistance and use data
	Incentives for research and development of new antimicrobials

Adapted from Okeke *et al.* (2005:570) and WHO (2001: 3-7)

During the 2011 World Health Day, the Director-General of WHO reiterated the urgency to take measures to reduce the spread of antimicrobial resistance. In her speech, she emphasised the need for coordinated effort, improving regulatory and supply chain systems, improving use of medicines by humans and animals alike and intensifying surveillance efforts. She stressed that unless action is taken today, there will be no cure tomorrow (WHO, 2011a).

2.2.7. Surveillance programmes

A key component of the WHO AMR strategy is the development of surveillance programmes to monitor trends in antimicrobial drug resistance and use. Surveillance involves the systematic collection and analysis of health-related data, and dissemination for decision-making on public health issues. For antimicrobial use it tracks both how antibiotics are being used and how much is being used (WHO, 2012b:13).

Essack (2006: 51b) defines the objective of surveillance as "*to facilitate the containment of antibiotic resistance by informing different strategies such as improved prescribing (rational drug use, a reduction in drug use, the implementation of dosing regimens based on drug pharmacokinetics and pharmacodynamics in different patient populations), the implementation of infection control policies and procedures, the development of or amendments to empirical therapy/standard treatment guidelines (STGs) and due vigilance in patients exhibiting classical risk factors for the acquisition of or colonisation with antibiotic resistant pathogens*".

AMR surveillance should be a two-pronged approach – monitoring of antibiotic usage and monitoring of resistance and linking these two together (WHA resolution of 2005; WHA Draft Global Action Plan, 2014:7, 13). Collection of surveillance data should be on-going and routine and should be collected at all levels of care – local, national, regional and global.

- At the local level, the data are used to formulate recommendations for rational use and standard treatment guidelines and for ensuring that health-care providers comply with recommendations.
- At national levels, data on resistance and use together inform policy decisions such as development or revision of essential medicines lists, and identify priorities for public health action, such as education campaigns or regulatory measures.
- At regional and global levels, surveillance data have proved to be invaluable advocacy tools in stimulating politicians and health-care providers into urgent action (WHO, 2012b:13)

Some methods of surveillance include:

i. Routine clinical microbiology data (antibiograms) (WHO, 2012b: 17; WHA, 2014:7)

   Data on AMR among local pathogens help define the best possible treatment for individual infections in patients. These data are useful for orienting treatment choices, understanding AMR trends, informing public health policy, identifying priority areas for interventions, and monitoring the impact of interventions to contain resistance (WHO, 2012b:10).

   Holloway *et al.* (2011b:374) in their pilot of community based surveillance of antimicrobials in resource constrained settings suggested that this was the most common method for monitoring resistance trends (WHO, 2009:9). This method is considered to be simple and less expensive as many facilities already perform antimicrobial susceptibility testing (CDC: 10; WHO 2009:9). Similarly, Lewis (2002:3) describes the method of routine collection of available laboratory data as the easiest and most convenient method of antimicrobial surveillance.

ii. Antibiotic usage data (WHO, 2012b:14)

   From the reference listed above, the WHO suggests reviews of prescriptions, sales data and pharmacy database as another method of antimicrobial use surveillance (WHO, 2012b:14). In a similar way, the National Antimicrobial

Utilisation Surveillance Program (NAUSP) based in South Australia uses the usage data from pharmacy dispensing records and patient admission records as the standard for their surveillance programme (South Australian Infection Control Service). Furthermore, Holloway *et al.* (2011a:153) in their pilot also employed two methods for surveillance of antibiotic use namely retrospective data reviews of prescriptions and bulk sales data and prospective data collection by exit interviews. Use of interviews in addition to database and prescription review is helpful in answering the question "why are antibiotics used", which cannot be answered from reviews of prescription if the diagnoses is not indicated on the prescription and sales data (WHO, 2012b:15, 19).

iii. Point-prevalence surveys (WHO 2012b:15)

These are snapshot surveys of antibiotic use. These provide more details regarding indications as compared to usage data mentioned above. Point prevalence surveys have been used extensively to document antibiotic use especially in hospital settings (Ansari *et al.*, 2009:1496-7). The European Surveillance of Antimicrobial Consumption (ESAC) project has used this method extensively and between 2006 and 2009 they coordinated three such surveys after which they concluded that such surveys are useful when time and resources do not allow for continuous surveillance and that if done repeatedly, point-prevalence surveys can be used to monitor trends in antimicrobial use (WHO, 2012b: 15; Zarb & Goossens, 2011). The National Antimicrobial Utilisation Surveillance Program (NAUSP) also identified Point-prevalence studies as an alternative surveillance method to their standard antimicrobial usage method (South Australian infection Control Service).

2.3. Resistance in Namibia

Not many studies on antimicrobial use and resistance in Namibia are documented. In studies carried out between 1997 and 2001 to monitor antibiotic use in Namibia, trends of increasing use in antibiotics in the public health sector were reported (Lates, 1999; Lates & Shiyandja, 2001).

Between December 2006 and February 2007, there was a cholera outbreak in the Kunene and Omusati regions in Namibia. A study to characterise this cholera outbreak isolates showed *Vibrio cholera* strains that were resistant to trimethoprim, sulfamethaxozaline and streptomycin (Smith *et al.*, 2008: abstract).

In 2007, in partnership with the Namibian Ministry of Health and Social Services and WHO Country Office for Namibia, the STI Reference Centre, which is a division of South Africa's National Health Laboratory Service (NHLS), participated in STI microbiological surveys at Windhoek and Oshakati to determine antimicrobial resistance in *Neisseria gonorrhoeae*. The reported prevalence of ciprofloxacin resistance was 24% overall (Oshakati 48%; Windhoek 5%). As a result of this survey, the Ministry of Health and Social Services revised the national STI treatment guidelines in 2008 and replaced ciprofloxacin with cefixime for the treatment of presumptive gonococcal infection. This study was part of the review of the evolution of *Neisseria gonorrhoeae* resistance to antibiotics in Africa (Lewis, 2011: 219).

In 2013, the results of a cross-sectional descriptive study aimed at assessing the antimicrobial sensitivity patterns of micro-organisms isolated from cerebrospinal fluid (CSF) to antibiotics commonly used in the empirical treatment of suspected bacterial meningitis in Namibia was published. The study found the most common pathogens to be isolated from the CSF to be *Streptococcus* species, *Neisseria meningitidis*, *Haemophilus influenzae*, *Staphylococcus* and *Escherichia coli*. These pathogens were shown to be highly resistant to penicillins and highly sensitive to cephalosporins (Mengistu *et al.*, 2013: 9-10).

In the same year, 2013, a report on the monitoring of the development of HIV drug resistance in Namibia through the use of early warning indicators was published. Early warning indicators assess the site and programme factors associated with the development of HIV drug resistance and they form a foundation of the WHO global HIV drug resistance (HIVDR) prevention and assessment strategy (Jonas *et. al.*, 2013:2).

All these studies were conducted in the public health sector. There are also no documented studies on how antibiotics are used in Namibia, nor reports of susceptibility data/trends. The purpose of this study is to gather evidence on how antibiotics are used in the private sector of Namibia. This thesis will specifically provide a landscape on the Namibia health sector in general and pharmaceutical management in particular.

As already mentioned before, antimicrobial use has been cited as the single most important factor responsible for increased antimicrobial resistance (Byarugaba, 2004:106). In their article on "*antimicrobial resistance determinants and future control*", Harbarth and Samore (2005:794) describe four categories that are determinants that drive the development, dissemination and control of antimicrobial resistance and the fourth category includes those factors at the macro-level that are related to the healthcare system which include regulatory environment. These factors are usually country specific and include, among other things, prescribing policies, reimbursement policies and healthcare regulation (health system and regulatory or policy framework). The South-East Asia regional strategy for prevention and containment of antimicrobial resistance argues that "resistance is a biological, behavioural, technical, economic, regulatory and educational problem and requires a comprehensive response" (Anon., 2010: 6). It is against this background that this paper will look at health systems in Namibia in general and specifically the management of antibiotic use to set the context in which to view antibiotic access, use and resistance in Namibia.

2.3.1. Namibia demographic and economic overview

Namibia is a sparsely populated country with a total land mass of 824 000km^2 and has a population of only two million with an estimated population growth of 2.5% per annum (WHO, 2010b: 1). The majority of the population resides in rural areas, specifically in the six northern regions of the country. The country is divided into 13 administrative regions with 33 health districts.

With a gross national income per capita of US$4 200 for 2008, the country has been recently reclassified as a middle-income country. However, the Gini coefficient of 0.6 demonstrates the inequalities faced by the country (MoHSS, 2010a:14), with

unemployment rates of 37% and at least 4% of the population considered extremely poor. Table 2-3 below summarises the Namibia geographic and socio-economic profile.

Table 2-3: Geographic and socio-economic profile

Indicator	Figure	Source
Population	2 104 000	Namibia 2011 Population and Housing Census, National Planning Commission 2012
Fertility rate	3.8 3.3	2006 Namibia Inter-census demographic survey, National Planning Commission World Health Statistics 2011
Life expectancy at birth	57	World Health Organization, 2012c: Namibia Health Profile
Under-5 mortality rate per 100 live births	69	Namibia Demographic Health Survey 2006/07, MoHSS, 2008b
Maternal mortality rate per 100 000 live births	449	Namibia Demographic Health Survey 2006/07, MoHSS, 2008b
% population with access to improved drinking water	88	Namibia Demographic Health Survey 2006/07, MoHSS, 2008b
% population with access to sanitation	34	Namibia Demographic Health Survey 2006/07, MoHSS, 2008b
Total expenditure on health	8.3	National Health Accounts, 2008, MoHSS, 2008c

WHO attributes the mortality rates mainly due to infectious diseases specifically pneumonia and diarrhoea diseases for under-5 and tuberculosis and HIV/AIDS for adults (WHO, 2011c:14–15). The same 2011 World Health Statistics report show that Namibia has an under-5 mortality rate of 47 per 1 000 live births.

2.4. Overview of health care in Namibia

2.4.1. Service delivery

The Namibia health system is characterised by two pillars, a dual health care system – the public and private health sector (profit and not-for-profit). In 2006/7, both the government and private health sector accounted for 8.3% of the total Gross Domestic Product (GDP) (MoHSS, 2008b:17). The public sector has adopted the principle of primary health care (PHC) as an approach for service delivery for the Namibian population. These approaches reflect all eight components of primary health care.

- Promotion of proper nutrition and adequate supply of safe water;
- Maternal and child care, including birth spacing;
- Immunisation against the major infectious diseases;
- Basic housing and basic sanitation;
- Prevention and control of locally endemic diseases;
- Education and training in the prevention and control of prevailing community health problems;
- Appropriate treatment for common diseases and injuries; and
- Active community participation in health and social matters.

The public health sector consists of the central, regional and district levels. The central level has devolved authority to the 13 regional directorates and 34 districts.

It is estimated that public health care facilities serve 85% of the Namibian population and is mostly accessed by lower income groups. The private for-profit healthcare system mostly serves the remaining 15% of the population, consisting of middle and high income groups (WHO, 2010b: 4). The ratio healthcare worker per population in Namibia is 3:1 000, which is slightly higher than the set WHO benchmark of 2.5:10 000 (O'Hanlon *et al.*, 2010:28; WHO 2012). However, the majority of these health care providers are in the private health sector with the public sector having less than two health care workers per 1 000 population (O'Hanlon *et al.*, 2010:28).

Tables 2-4 and 2-5 below show the health facilities as well as health professionals in Namibia across the two sectors.

Table 2-4: Distribution of health facilities between public and private sector

Facility type	Public	Private
Hospitals	34	13
Primary health care clinics	265	75
Health centres	44	8
Private provider consulting rooms	N/A	557
Private pharmacies	N/A	75
Total	333	844

Source: O'Hanlon *et al.* (2010: 37) and MoHSS (2010b)

Table 2-5: Distribution of healthcare workers by sector

Category	# registered 2006/2007	Public sector		Private sector	
		Number	%	Number	%
Doctors	774	216	28	558	72
Registered nurses	2,989	1,626	54	1,363	46
Enrolled nurses	2,761	1,884	68	877	32
Pharmacists	239	27	11	212	89
Pharmacist assistants	137	65	47	72	53
Social workers	250	76	30	174	70

Source: O'Hanlon *et al.* (2010:29), WHO (2011:120)

2.4.2. Burden of disease

Infectious diseases remain the major contributor to the burden of disease in Namibia. WHO reports that 63% of all years of life lost in Namibia are caused by communicable diseases (WHO, 2012c). Other contributors are diseases related to pregnancy and delivery and infant and childhood (MoHSS, 2005:8; MoHSS, 2010b:3). According to the National Health Account of 2008, Namibia faces high infant and under-5 mortality rate, as well as high maternal mortality, the former attributed to, among others, immediate causes such as diarrhoea, pneumonia, malaria, and perinatal causes and underlying issues such as malnutrition and HIV/AIDS (MoHSS, 2008a:4). The same report suggests that major causes of outpatient visits among the under-5 children are infections (respiratory, skin, and gastrointestinal), malaria and trauma/injury.

In the recent past, leading causes of death in the country have been reported to be HIV/AIDS, diarrhoea, pulmonary tuberculosis (TB), pneumonia, and malaria (MoHSS, 2008c:25). The World Health Statistics report also shows malaria, tuberculosis, pneumonia, HIV/AIDS and diarrhoea as major contributors to the burden of disease in Namibia (WHO, 2011b: 61-86). Other leading causes of mortality are other respiratory system diseases, anaemia, heart failure, malnutrition, and hypertension. The Health Information System (HIS) data also reveal a growing threat of non-communicable diseases (NCDs) (MoHSS, 2008b:4).

2.4.3. Private health care in Namibia

The private health sector is defined as providers and facilities for health that are outside the public health system. Namibia has a robust, very active and well organised private health sector, which because of colonial history closely resembles that of neighbouring country, South Africa (Brockmeyer, 2012: 3). The private sector is regulated by the Hospital and Health Facilities Act (36 of 1994). The sector comprises private hospitals, private clinics, doctors, nurses, pharmacists and social workers. The total value of the private sector market in 2008/09 was reported around N$1 296 802 073 (US$144 410) with 25% spent on dispensed medicines. As shown in tables 2 and 3 above, the private sector has 844 health facilities and two thirds of all doctors as well as 89% of all

pharmacists. These resources are mostly distributed in the urban areas (O'Hanlon *et al.,* 2010:29).

The private sector services 15% of the population (WHO, 2010b) and most of the financing in the private sector is through the health insurance. The health insurance industry in Namibia is well developed and organised into medical aid funds. Medical aid is available to only the formally employed and mainly middle and high income earners (PharmAccess Foundation, 2011: 26). Namibia has 10 medical aid funds, six closed and four open funds. These funds are regulated by the Namibia Association of Medical Aid Funds (NAMAF), a juristic body, established in terms of the Medical Aid Funds Act, 1995 (Act 23 of 1995) to control, promote, encourage and co-ordinate the establishment and functioning of medical aid funds in Namibia. At their annual conference in 2011, NAMAF reported 368 601 people on medical aid (NAMAF conference, unpublished).

The national health and HIV/AIDS resource tracking exercise conducted in 2010 reported the contribution of the private sector in financing health to be 22.3% of the Total Health Expenditure (THE) for the fiscal year 2008/09 (MoHSS, 2010c:18). The same report showed that 10.7% of THE was spent on pharmaceuticals obtained directly from retail pharmacies while 27.5% of all out of pocket household expenditure was reported to be spent on pharmaceuticals (MoHSS, 2010c:27). For the 2011/12 financial year, it is estimated that the public sector spent 43 627 122.19 on antibiotics (key informant interview). However, there is no documented and published data on antibiotic spending in the private sector.

2.4.4. Management of antibiotics in Namibia

The overall management of medicines in Namibia is regulated by the Medicines and Related Substances Control Act (13 of 2003) and the National Medicines Policy (MoHSS, 2011a).

2.4.5. The National Medicines Policy

The National Medicines Policy (NMP) for the Republic of Namibia provides comprehensive guidelines and development objectives for the Namibian public and

private pharmaceutical sectors within the broader framework of the Government's health policy and development plans. The policy addresses factors that impact on delivery and use of pharmaceuticals in both the public and private sector such as legislation and regulation; drug procurement and distribution; the appropriate use of drugs by health workers and consumers; human resources development; and drug pricing and financing. The first policy document was published in 1998. The policy provides a framework within which the activities of the pharmaceutical sector can be coordinated. It covers both the public and the private sectors, and involves all the main stakeholders in the pharmaceutical sector. The policy was revised in 2011.

Some specific objectives of the NMP are to (MoHSS, 2011a:5):

- Strengthen the quality assurance system to guarantee the safety and efficacy of medicines supplied to clients in both public and private sectors;
- Strengthen the medicines supply management system through improved procurement, storage and distribution at all levels of the health care system;
- Promote the rational use of medicines by prescribers, dispensers and clients;
- Contain the emergence of Antimicrobial Resistance (AMR). (MoHSS, 2011a:5)

2.4.6. Medicines regulation

The regulation of the use of medicines is Namibia is done through the Namibia Medicines Regulatory Council (NMRC), a statutory body established in terms of the Medicines and Related Substance Control Act (13 of 2003). The Act was promulgated in 2008. Prior to that, the regulation of medicines was governed by the Medicines and Related Substances Control Act (101 of 1965), a South African law. There are four sections under the NMRC, that is, inspection and licensing, medicines registration, quality surveillance laboratory and the therapeutic information and pharmacovigilance centre (NMRC website).

As prescribed in the Act, medicines can only be imported into and sold in Namibia if they are registered in Namibia. Medicines can only be imported by licensed persons and can only be sold by pharmacists or authorised persons who are lawfully performing

health services (medical doctors and nurses). To ensure tighter control of imported medicines, the importation of medicines in Namibia is restricted to registered medicines wholesalers in the country (NMRC Website; NMRC staff interview).

Antibiotics in Namibia are classified as schedule 2 and therefore they can only be sold upon a prescription from an authorised prescriber (Medicines and Related Substance Control Act, 13 of 2003).

The Inspection and licensing section of the NMRC is responsible for compliance and enforcing the Medicines and Related Substance Control Act (13 of 2003). This is done through:

- Collection of samples from distribution outlets for examination to ensure that standards are maintained post registration (i.e. monitoring counterfeits).
- Inspection of pharmacies, dispensing medical practitioners, hospitals and all health facilities to ensure compliance with the law regarding the sale and use of medicines.
- Visiting all border posts to ensure that only registered medicines are imported and that importation is done by licensed manufacturers and wholesalers/distributors.
- Inspection of general retail outlets to ensure that medicines are sold only by authorised persons and in authorised premises (NMRC).

The inspection team undertakes routine visits to facilities, mainly the public facilities. There have not been reports from the NMRC on counterfeit medicines in the country (stakeholder interview).

The quality and surveillance laboratory is responsible for ensuring the quality of medicines in the country. Routine tests are carried out on medicines arriving at the government's Central Medical Stores to ascertain the quality and efficacy of the medicines. This implies that medicines coming into the private sector are usually not tested to ensure quality and efficacy. Coupled with the fact that most inspection visits are conducted in state facilities, there is likelihood that counterfeit medicines in the

private sector will go undetected. Additionally, the laboratory analyses received samples with dossiers for registration as well as samples collected during inspections. The other function of the laboratory is to conduct post marketing surveillance activities (NMRC).

Namibia, however, has limited capacity to conduct routine surveillance including border controls and facilities monitoring to ensure that medicines in the country are registered medicines and routine tests to identify counterfeit medicines (stakeholder interview).

The Therapeutic Information and Pharmacovigilance Center (TIPC) was established in 2007, and launched in 2008, with the dual function of providing therapeutics information to the public and health care professionals and coordinating pharmacovigilance (PhV) activities (NMRC). It is the 90th full-member country in the WHO's international medicine monitoring programme. The aim of the centre is to improve rational use of medicines available in the country and to contribute to their safe use. The information gathered through TIPC has been used to provide advice on medicines use in the country and provide guidance to treatment guidelines. The information collected is used to generate signals (areas of concern) and where an apparent signal is detected, further investigations are conducted and the information is used to provide guidance on guidelines. TIPC also collects safety update data from other sources and presents such information with recommendations to the NMRC clinical committee for regulatory action. To ensure proper reporting by the public and health workers, National Guidelines for Medicines Safety Surveillance were developed in 2011 (MoHSS, 2011b:6). Some of the regions have further conducted pharmacovigilance training but these were geared at public sector practitioners. The presence of the TIPC can be said to have sensitised regions and facilities to adverse drug reactions (ADR) reporting and medication errors as these are now routinely discussed in most Therapeutics Committees (stakeholder interview).

2.5. Rational use

Rational use of medicines refers to the correct, proper and appropriate use of medicines whereby a patient receives the appropriate medicine, in the correct dose for an adequate period of time and at the lowest cost to them (WHO, 2010c). The WHO further describes irrational use of medicines as a global problem with at least 50% of all medicines prescribed, dispensed and used inappropriately. Antimicrobial resistance is considered one of the consequences of inappropriate or irrational use of medicines (WHO, 2010c).

In accordance with WHO guidelines, Namibia developed Namibia Essential Medicines List (Nemlist), which was initially launched in 1995, to serve as a guide for medicine prescribing and management to health workers within the public service. The Nemlist contains an essential list of pharmaceuticals that are considered adequate to treat majority of public health conditions prevalent in Namibia. Selection of medicines into the Nemlist is based on clinical practice, internationally recognised treatment standards and cost. The 5th edition of the Nemlist was launched in October 2012. Limiting the availability and use of medicines through the Nemlist is a strategy to improve rational use of medicines. Similarly, restricting the use of antibiotics by limiting both what is available and how it can be used is a strategy for antibiotic management to reduce the development of resistance (WHO, 2001:5).

The medicines on the Nemlist are listed according to generic name and the list is arranged broadly in 14 main sections according to the International Anatomical Therapeutic Chemical (ATC) classification system to enable users to identify the required items in the appropriate category. The medicines are further classified according to level of use and VEN classification (vital, essential or necessary) (MoHSS, 2008d:3).

Use of the Nemlist, however, is implemented only in the public sector while the private sector has no restriction in the choice of medicines selected. The main restriction in the

private sector comes from the insurance (medical aid) industry, which mainly promotes the use of generic medicines (stakeholder/personal interview).

In 2011, Namibia launched the first edition of Standard Treatment Guidelines (STG), which was developed as a collaborative effort between public and private sector health practitioners. The purpose of the STG is to promote use of medicines in a rational manner in accordance with the essential medicines concept which is aimed at ensuring availability of safe and efficacious medicines by rationalising the procurement, distribution, prescribing and dispensing of medicines. (MoHSS, 2011c: xxiv). Prior to these STGs, Namibia relied on the Treatment Manual for Clinics and Pocket Manual for Health Workers published in 1992 and 1996, respectively.

Treatment of diseases in the private sector is less regulated than in the public sector. While guidelines are meant to be used in both sectors, their use is not enforced in the private sector. The medical aid schemes (funds) often have their own guidelines, mainly for chronic diseases, which they try to apply. However, this often proves to be difficult as doctors can still insist on a particular treatment and the medical aid still reimburses this. Apart from these guidelines, there is not much restriction imposed on private practitioners on what they can prescribe or dispense apart from the use of generic medicines (stakeholder interview).

In addition to Nemlist and STGs, Namibia also instituted the concept of Therapeutic Committees (TCs) in the public facilities. The role of the TCs is to monitor and promote rational use of medicines. Prior to the development of the STGs, many TCs developed their own antibiotic policies aimed at controlling the use of antibiotics in their respective facilities. Like with the Nemlist, TCs as a concept is implemented only in public facilities (stakeholder interview).

In 2005, Namibia, with support from the Rational Pharmaceutical Management Plus programme, conducted a regional Promoting Rational Drug Use in Namibia. This provided members of TCs and pharmacists with the skills and knowledge necessary to

monitor medicines usage in their facilities. This course was again open to and attended only by public sector health workers (Chalker *et al.,* 2005:1).

Identifying the need to improve rational use of medicines, the Ministry of Health and Social Services and the University of Namibia embarked on a journey to establish the INRUD chapter in Namibia. INRUD is the International Network for Rational Use of Drugs. It was established in 1989 to design, test, and disseminate effective strategies to improve the way drugs are prescribed, dispensed, and used, with a particular emphasis on resource poor countries (INRUD website). Discussions have been under way since 2008 between the University of Namibia, TIPC and INRUD to start an INRUD chapter in Namibia (stakeholder interview).

Namibia has made monitoring medicines use a part of routine work. Between 1997 and 2001, three Medicines Use Surveys were conducted to determine the use of medicines in health facilities. These surveys were conducted only in the public health facilities and not extended to the private sector. It is important to note that these surveys demonstrated an increase in antibiotic use from 39% in 1997 to 51% in 2001 (Lates & Shiyandja 2001:10). Additional to these surveys, the Division: Pharmaceutical Services through the pharmacy management information system (PMIS), which was launched in 2007, routinely monitors, among other things, medicines availability as well as antibiotic usage. These data are collected and reported on quarterly or semi-annually (Phulu *et al.*, 2012:1). The June 2012 PMIS report shows that in the public sector there has been a decrease in percentage of out-patient prescriptions containing an antibiotic from 59% in Oct 2009 to 44% in March 2012 (Phulu *et. al.,* 2012: 23).

While strategies are in place to ensure regulation of medicines in Namibia, most of these are only applied in the public sector thus rendering the private sector less regulated. With less regulated private sector and no surveillance there are greater chances of inappropriate use of medicines including antibiotics.

2.6. Antibiotic resistance monitoring in Namibia

There is no literature evidence that suggests that there are formal means of monitoring and reporting antimicrobial resistance in Namibia. In 2005, the Namibia Alliance for Prudent Use of Antibiotics (APUA) chapter was founded and launched. However, the chapter has been inactive since. In the same year, APUA/Namibia arranged for the installation of WHONet at the Namibia Institute of Pathology (NIP) laboratory and at the PathCare laboratory (personal interview).

WHONet is software that was developed for the management of routine laboratory results and focuses on data analysis, particularly of the results of antimicrobial susceptibility testing. The software allows for analysis of laboratory findings including isolate line listings, antimicrobial susceptibility test statistics, studies of multidrug resistance patterns, and hospital and community outbreak detection. The purpose of the installation of WHONet was to enable the country to monitor and report on sensitivity patterns routinely (WHO).

PathCare monitors and reports on sensitivity patterns on their website every 6 months and also has an antibiotic guide on their website. It is important to note that the results from PathCare may be an under/overestimation, depending on the sampling strategy employed. Also, PathCare does not operate in every town in Namibia therefore the results do not cover the whole private sector. It is not clear if this information is routinely accessed by medical practitioners and whether it is used in managing patients. Again in the public sector, there is no evidence of reported sensitivity data. Currently, the TIPC is undertaking an activity with NIP of analysing antimicrobial sensitivity patterns in the public sector. The purpose of this activity is to see if current STGs are in line with local sensitivity patterns (Mengistu, 2013).

2.7. Chapter summary

This chapter expounded the literature on antibiotic resistance including the impact, spread and strategies for stewardship. The chapter further explored the Namibian

health system specifically the policy and legal framework that influence antibiotic use and the monitoring and management of antibiotic resistance.

The next chapter will present the findings of the study in four articles.

Chapter 3: Manuscripts

3.1. Manuscript 1

In this section, the following manuscript titled “Surveillance of antibiotic use in the private sector in Namibia using sales and claims data” is presented. The paper was submitted for review to the **Journal of Infectious Diseases in Developing Countries** and prepared in accordance with the *Author Guidelines* of the said journal (provided in Annexure F).

The author guidelines are also available from http://www.jidc.org/index.php/journal/about/submissions.

The references for this manuscript are provided at the end of the manuscript.

The article has been accepted for publication (communication from the journal is attached in Annexure G).

Surveillance of Antibiotic Use in the private sector in Namibia using sales and claims data

Dawn D Pereko[1], B. Pharm, MPH, PhD student, Medicine Usage in South Africa, Faculty of Health Sciences, School of Pharmacy, North-West, University, Potchefstroom, South Africa.

Email: dineopereko@gmail.com

Martie S. Lubbe, B. Pharm, M. Pharm, PhD, Professor, Leader, Medicine Usage in South Africa, Faculty of Health Sciences, School of Pharmacy, North-West University, Potchefstroom, South Africa

Email: martie.lubbe@nwu.ac.za

Sabiha Y. Essack[2], B. Pharm, M. Pharm, PhD, Professor, Dean, School of Health Sciences, University of KwaZulu-Natal, Durban, South Africa.

Email: essacks@ukzn.ac.za

Running title: Antibiotic use and Namibia private sector

Key words: antibiotics, antibiotic use, Namibia, private sector, claims data, wholesale data

Corresponding author: Dawn D. Pereko

P.O. Box 35209, Windhoek, Namibia

Tel: + 264 61 232873, Fax: +264 61 231273

M: +264 81 249398
dineopereko@gmail.com

---

[1] Corresponding author: Dawn D Pereko, P.O. Box 35209, Windhoek, Namibia Tel: + 264 61 232873, Fax: +264 61 231273; M: +264 81 249398; dineopereko@gmail.com

[2] Member of the Global Respiratory Infection Partnership (GRIP) sponsored by Reckitt and Benckiser

Abstract

Introduction: Antibiotics are among the highest prescribed and used therapeutic agents for human use globally and their use has been associated with the development of resistance. The study objective was to identify sources for quantifying antibiotic usage patterns and to assess such use in ambulatory patients in the private health sector of Namibia.

Methodology: A retrospective analysis of prescription claims data and sales data for the period 2008 to 2011 was conducted. Antibiotic use was expressed in number of antibiotic-containing prescriptions and volume of units sold and then standardised using defined daily dose per 1000 inhabitants per day.

Results: Antibiotic usage was highest among females (53%) and the age group 18-45 years (41%) and in Windhoek, the capital, (34%). Overall, wholesale data showed higher antibiotic use than prescription claims data. However, both sources showed similar patterns of antibiotic use. Penicillins were the highest used pharmacological group with amoxicillin and clavulanic acid combination (8.25 DID claims; 8.32 DID wholesale) being the highest used of the agents.

Conclusion: Antibiotic use in the private sector of Namibia is comparable to that of high consuming European countries such as Italy. Trends observed in this study were decreases in the use of narrow spectrum antibiotics in favour of broad spectrum and newer antibiotics. Since this was the first study to assess antibiotic use in the private sector of Namibia, it could serve as a starting point for continued monitoring of antibiotic use in the whole Namibia in the context of the WHO Global Action Plan to contain antibiotic resistance. Prescription claims data are important in the estimation of antibiotic use in the private sector of Namibia.

Key words: antibiotics, antibiotic use, Namibia, private sector.

Introduction

Infectious diseases account for 15 million deaths per year globally equivalent to 43% of global burden of disease [1]. Up until recently, the management of these diseases has been made easier by antibiotics [2-3]. As a result, the use of these drugs has become widespread such that they have become the most widely prescribed agents globally [4] in both the developed and developing countries [5-7] including Africa [8; 9].

The biggest concern with the high use of antibiotics is the development of antibiotic resistance. High exposure to antibiotics is cited as the most important cause -that can lead to resistance [10; 11]. Numerous studies in this aspect have elucidated the relationship between antibiotic use and resistance development [12; 13].

Namibia has a dual healthcare system with 82% of the population seeking health care in the public sector and 18% in the private sector. The majority of the health providers particularly doctors (72%) are practising in the private sector.

Antimicrobial surveillance is considered a cornerstone in promoting antimicrobial stewardship and the control of resistance development [14]. The WHO 2011 Policy Package and Global Action Plan to combat antimicrobial resistance [15; 16] advocates for monitoring volumes and patterns of antibiotic use as part of the surveillance. No such surveillance has been carried out in the private health sector of Namibia.

The objective of this study was to identify and/or evaluate data sources for quantification of antibiotic usage patterns and to assess such use in ambulatory patients in the private health sector of Namibia.

Method

Ethical clearance

Ethical clearance for this study was obtained from the Research Ethics Committee (Human), Faculty of Health Sciences, North-West University (Ethical clearance number NWU-00028-13-s1). Additionally, permission to use the data for the study was provided along with the data by the participating medical insurer, their medical fund administrator and wholesaler.

Study design

The study was a retrospective drug utilisation review in which data on antibiotic prescription claims and wholesale sales were collected and analysed. Data collection was in December 2011 and covered a 4-year period dating back to 1 January 2008. The prescription claims data were obtained from a medical aid fund that represented 55% of the Namibia population covered by medical aid. The wholesale data were obtained from one of the two leading wholesalers in the country. Only data related to antibiotics for systemic use (anatomical therapeutic classification (ACT) J01) were collected and analysed.

The ACT/daily defined dose (DDD) methodology was used to evaluate the consumption of antibiotics. Each antibiotic in both databases was assigned a DDD obtained from the WHO ACT/DDD index 2013 (www.whocc.no/act_ddd_index). For wholesale data, the DDD was

calculated as unit strength x pack size x quantity sold/ DDD assigned. The prescription claims and wholesale sales data were expressed as DDD/1000 population/day using the formula:

DDD/1000/day = (Total consumption in DDDs/Total population covered x Total days in the period of data collection) x 1000.

The population used for the prescription claims data was the population of the people covered by the medical aid fund for each year. For the wholesale data, the population of the country that was estimated to be serviced by the wholesaler was used. Number of days used were 365 days.

Data analysis

The data were received from the suppliers on Microsoft Excel® 2010 format. No other manipulation was done besides removing antimicrobials that were not antibiotics and also adding the ACT and DDD classifications.

Microsoft Excel™ and SAS Version 9.1.3 (SAS Institute, Cary, NC) were used for analysis. Descriptive statistics were used to understand frequencies and in the claims data to describe patient and provider variables. All statistical significances were considered with probabilities of $p < 0.05$. The practical significance of the results was computed when a *p*-value was statistically significant ($p \leq 0.05$). Chi-square test ($\chi 2$) was used to determine if an association existed between proportions of two or more groups (e.g. age groups, gender, and dispenser, towns and generic indicator). The Cramer's *V* statistic was used to test the practical significance of this association (with Cramer's $V \geq 0.5$ defined as practical significance).

Results were presented in volume of antibiotic prescriptions dispensed, units of antibiotics sold and DDD/1000/day of antibiotics consumed.

Results

A total of 1,129,053 antibiotic-containing prescription claims were made and 842,800 units of antibiotics sold during the 4-year study period with an overall increase in antibiotic use being observed. . The claims data showed a 25% increase in antibiotic prescriptions while the wholesales data showed a 57% increase in unit sales over the 4 years.

Wholesale data did not have any demographic details (such as age and gender of patients) and demographic findings presented below were based on the analysis of the claims data only and are reported in prescriptions volume.

Age and gender distribution of patients

More females (53%, n=604,334) than males (47%, n=524,869) received antibiotics over the 4-year period under review (p<0.0001; Cramer's V=0.0424). This trend was observed also for most individual antibiotics with the exception of benzathine penicillin and procaine penicillin where more males (56%, n=1,095; 57%, n=222) than females (44%, n=897; 43%, n=170) received these drugs. Refer to additional data, table 1 for more information.

The highest number of consumers of antibiotics was in the age group ≥18 to ≤45 years (41%, n=458,668), followed by the 45–65 year age group (28%, n= 319,581) (p<0.0001; Cramer's V =

0.1025). The least number of consumers of antibiotics were those older than 65 years followed by the teenagers (≥12 to ≤18 year olds).

For individual antibiotics, similar trends as overall consumption trends by age were observed except with cefpodoxime, which was dispensed mainly to paediatric patients (age group 0 to ≤12 years; 66%, n= 22,582). Refer to additional data, table 2 for more information.

Antibiotic use by dispenser

Fifty-four percent (54%, n=612,440) of antibiotic prescriptions was dispensed by pharmacists and 46% (n=516,750) by medical doctors (p<0.0001; Cramer's V=0.1093). Most of the injectable antibiotics were dispensed by doctors. There were no other significant differences between the two dispenser types.

Seventy-seven percent (77%; n=857,817) of all antibiotic prescriptions was generic. The prevalence of generic dispensing was nearly the same between doctors and pharmacists (p<0.0001; Cramer's V =0.2154). Refer to additional data, table 2 for more information.

Antibiotic use by town

Five towns in Namibia accounted for 60% of all consumption of antibiotics nationally. Windhoek, the capital, accounted for just over a third of all antibiotic consumption. With the exception of the top five towns listed below, there was no difference between rural and urban towns in terms of antibiotic consumption (p<0.0001; Cramer's V = 0.1126). Table 1 below shows the top 5 towns that are the highest antibiotic consumers nationally.

Table 1: Top 5 antibiotic consuming towns

Town	Antibiotic consumption (n) (# of prescriptions) (N=1,129,220)	Consumption % (N=1,129,220)
Windhoek	381, 611	34.00
Oshakati	113, 173	10.00
Ondangwa	80, 047	7.09
Rundu	68, 518	6.07
Katima Mulilo	38, 190	3.38

Throughout all the towns, the trends in antibiotic choices were the same as the national trend presented below under pharmacological groups.

Cost of antibiotics

The total cost of antibiotics as calculated from the prescription claims database per year was R26, 941,120 (USD3,326,064) in 2008. This increased to R43, 711,348 (USD 5,828,180) in 2011. For each study year, antibiotics accounted for 46% of the total cost of antibiotic-containing prescriptions. There was no data on total cost of all medication therefore antibiotic cost as a percentage of total medicine cost could not be calculated.

The cost of 10 most used antibiotics was calculated. These cumulatively accounted for 80% total antibiotic costs in each year. Refer to additional data, table 4.

Antibiotic consumption expressed as DDD/1000/day

Both wholesale and claims data showed similar trends in antibiotic use. Overall antibiotic consumption from claims data was 28.2, 25.6, 25.3 and 29.2 DDD/1000/day in 2008, 2009, 2010 and 2011, respectively. From wholesale data, antibiotic consumption showed increases from 19.0

to 22.11, 29.05 and 35.41 DDD/1000/day in each of the years, respectively. These changes in consumption, however, were not statistically significant (p=0.988). Table 2 shows overall antibiotic usage by antibiotic group over the 4-year period by prescription claims and wholesale data.

Table 2: Antibiotic use by class over the four year period expressed as DDD/1000/day by prescription claims and wholesale data

Antibiotic Group	ATC*	Claims Data		Wholesale Data	
		DDD	%	DDD	%
Penicillin	J01C	11.19	41.77	12.5	38.88
Cephalosporins	J01D	5.28	19.70	6.9	21.52
Macrolides	J01F	4.99	18.64	4.6	14.24
Aminoglycosides	J01F	0.08	0.29	0.1	0.16
Tetracyclines	J01A	1.99	7.43	4.3	13.30
Quinolones	J01M	2.68	10.00	3.5	10.84
Chloramphenicol	J01B	0.01	0.03	0.0	0.00
Other Beta lactams	J01D	0.49	1.83	0.0	0.12
Other	J01X	0.09	0.32	0.3	0.94
Total		26.78	100.00	32.0	100

*ATC denotes the anatomic therapeutic classification of the WHO

Both sources showed penicillins to be the most used antibiotic class, accounting for 42% and 39% of all antibiotic use for claims and wholesale data, respectively. These were followed by cephalosporins, macrolides, tetracyclines, and quinolones. Claims data showed a decrease in the use of penicillins while wholesale data showed an increase in sales of the antibiotic over the 4-year period. All other antibiotic groups showed an increase in use in both claims and wholesale data with exception of aminoglycosides, which showed a decrease on claims data and no change on wholesale data.

Substantial increase in usage was observed with the macrolides due to high increase in azithromycin use from 0.278 DID in 2008 to 1.35 DID in 2011 (0.64 DID in 2008 to 1.45 DID in 2011 for wholesale data).

The top nine antibiotics based on sales volume and number of prescription claims are presented in Table 3.

Table 3: Top 9 highest consumed antibiotics over a 4 year period expressed as DDD/1000/day (DID)

Antibiotic	Claims Data		Wholesale Data	
	DID	%	DID	%
Amoxicillin	1.67	6.85	3.45	12.31
Amoxicillin + Clavulanic acid	8.35	34.25	8.32	29.69
Azithromycin	1.63	6.69	1.51	5.39
Cefpodoxime	0.27	1.12	0.363	1.30
Ceftriaxone	0.04	0.16	0.14	0.50
Cefuroxime	5.94	24.35	6.23	22.23
Ciprofloxacin	1.55	6.36	2.45	8.74
Clarithromycin	3.2	13.13	1.51	5.39
Doxycycline	1.73	7.10	4.05	14.45
Total	24.38	100.00	28.02	100.00

In all the years under review, both sources of antibiotic consumption computations from wholesale and claims data showed amoxicillin/clavulanic acid combination as the most used antibiotic, accounting for about a third of all antibiotics used. This was followed by cefuroxime and clarithromycin from claims data computations. From consumption figure calculations using

wholesale data, doxycycline was observed to supersede clarithromycin in quantities consumed per year (Table 3).

The macrolides azithromycin and clarithromycin showed substantial increases in use while the use of ciprofloxacin stayed constant throughout.

Discussion

This was the first study to assess antibiotic use in the Namibian private health sector. Depicting same trends as reported globally, the study showed increases in antibiotic consumption over the 4-year period under study. The 25% increase observed in the consumption of the agents within the private health sector, however, is lower than the 36% global increase reported by Van Boeckel *et al.* [7]. Windhoek, among the towns and cities studied for their antibiotic consumption, had the largest associated antibiotic consumption figure. This finding was not surprising, the city being the capital of Namibia and having the majority of private health care services (63% of the doctors and 45% of pharmacies).

Consumption was observed more with females than with males. This could be due to the fact that females generally have a higher health-seeking tendency than males and that there are more female beneficiaries covered by medical aid than there are males [17].

The overall antibiotic consumption over the total study period in the Namibia private sector was 26.8 DDD/1000/day. This figure is comparable to some European countries as reported by the European Surveillance of Antimicrobial Consumption (ESAC) project in 2010. Namibia is comparable to Italy, Luxembourg and France [18] and can be considered by the ESAC

classification as a high antibiotic consumer. According to the ESAC classifications, countries with consumption figures of <16.7 DID are considered low consumers; between 16.7 and 22.38 DID medium consumers and >22.38 DID high consumers [18].

This observed high and increasing antibiotic usage in the Namibian private sector is worrisome. While antibiotic use has increased by 25% over four years, there has not been a corresponding increase in the population that could explain the reason for the increase in use. This implies that the same population is having greater exposure to greater quantities of antibiotics thus making for greater selective pressure favouring the development of resistance. It would be important to understand further what the factors contributing to this antibiotic use are in order to design targeted interventions to improve prudent use of the agents.

In addition to increased overall antibiotic use, our study uncovered significant trends in antibiotic usage patterns that established within the private health sector an increased use of broad spectrum antibiotics, which paralleled a decrease in use of narrow spectrum antibiotics and an increased preference for newer antibiotics. Our data also showed that outpatient care within the sector was highly dependent on three classes of antibiotics, namely, the penicillins, the cephalosporins and the macrolides – and mainly on the broad spectrum agents in these classes. These findings are not unique to Namibia but have been reported by others also. Lee and colleagues reported general increases in the use of broad spectrum antibiotics in the United States of America [6] similar to findings of this study. Their study reported the USA as having an "unprecedented high" use of broad-spectrum antibiotics. Similar results were also reported in Malta [19], Israel [20], India [21], Italy [13]; and in Europe and Eastern Europe [22-23]. South

Africa, which has a very similar health system to Namibia, has also been reported as having an increased use of broad-spectrum antibiotics [7, 31].

This high use of broad spectrum and newer antibiotics is a cause for concern since increased use of broad spectrum antibiotics has been associated with the development of cross resistance to other agents in the same class, compromising the use of the antibiotic class as a whole [19, 20, 24]. In this era where there are few antibiotics in development, the greatest concern with the development of resistance is that it could lead to a situation where health care professionals will not have appropriate medications to effectively treat infections [25-28]. It is therefore of utmost importance that antibiotics are used prudently in order to ensure their long-term availability and effectiveness.

The observed situation in Namibia calls for immediate public health interventions. Measures such as the introduction of antibiotic prescribing guidelines; continuing professional development sessions on antibiotic usage data and education on local sensitivity patterns should be considered. Namibia has national Standard Treatment guidelines. However, their use is not enforced in the private sector. Local sensitivity data are also available but the health providers do not seem to be aware of these. Activities aimed at educating the patient on antibiotics and their proper use should also be explored. In 2013, the Pharmaceutical Society addressed the issue of Antimicrobial Resistance during Pharmacy Week. Beyond this, there have not been dedicated national efforts to educate patients on antibiotics and their use.

In this study, two sources employing claims and wholesale data in estimating antibiotic usage in the private health sector were compared. Both sources showed similar trends in antibiotic usage but computations using wholesale data showed higher consumption of antibiotics as compared to claims data, indicating an overestimation of consumption figures. This finding is consistent to what is reported by other studies that employed similar comparative methodologies [22, 29, 30]. Medicines claims data is closest to consumption, as it is based on the actual scripts dispensed. Wholesale data includes stock that could be on the shelves, expired at the pharmacies, breakages or not sold and some of these could account for the overestimation.

In our study, we found claims data more reliable and more informative in terms of patient and provider profiles. We would therefore recommend that future studies use claims data to quantify antibiotic usage. A main concern raised by other authors regarding claims data is that they do not cover over-the-counter antibiotic sales [29, 30]. This should not be a major concern in Namibia since by law; antibiotics are not sold without prescription. Using claims data can more accurately reflect antibiotic use in that data used in calculations have been validated by the medical insurer and are also close to actual consumption data, i.e. actual quantities dispensed to the patient. Wholesale data in comparison represent antibiotics sold to the dispenser and not necessarily what is sold to the patient.

The limitations of this study were that data provided, firstly, were annual data which did not allow for analysis to determine monthly trends and seasonal variations in antibiotic use. Data sources, secondly, did not contain information on clinical indications for which the antibiotics were prescribed. This did not enable an evaluation of the appropriateness of the prescriptions to

establish whether the observed high use of antibiotics in the private health sector was appropriate or not. Thirdly, Namibia has a dual health system the public and private health systems. The study was intended to determine antibiotic use in the private sector and the findings as such cannot be generalized to depict the entire country situation.

Conclusion

Routine surveillance of antibiotic usage is an important step in antimicrobial stewardship. It generates valuable information for the formulation of policies on antibiotic use to improve appropriate prescribing and use of the agents to curb resistance development.

The study uncovered very high antibiotic use in the private sector of Namibia, particularly high use of broad spectrum antibiotics. These findings are comparable with results of similar studies conducted in Europe and elsewhere on the African continent. The study also found claims data to be better than sales data in quantifying antibiotic use.

The findings of this study apply to a small fraction of the Namibian population accessing care in the private sector and do not provide a full picture of antibiotic consumption nationally. We recommend further studies that aim at estimating antibiotic usage patterns in both the public and private health sectors to reflect the national situation. We also recommend studies that similarly aim at investigating patterns of antibiotic resistance development and the effects of antibiotic use on such resistance development patterns. The results of such studies will provide baseline information required for the formulation of antibiotic usage policies to promote an appropriate use of the agents and a curbing of resistance development.

Competing interests

The authors declare that they have no competing interests

Acknowledgements

The authors wish to acknowledge the medical aid fund and administrators and wholesale that provided the data for this study.

There was no funding for this study.

References

1. Head MG, Fitchett JR, Cooke MK, Wurie FB, Hayward FC, Atun R (2013) UK investment in global infectious disease research 1990 – 2010: a case study. *The Lancet Infectious Disease.* 355 – 364.
2. Alanis AJ (2005) Resistance to antibiotics: are we in the post antibiotic era*? Archives of Medical Research.* 36: 697–705. Available at http://www.ncbi.nlm.nih.gov/pubmed/16216651. Accessed 05 April 2011.
3. Cartlett J, Callignon P, Goossens H, Gyssens I, Harbarth S, Jallier V, et al. (2011) Society's failure to protect antibiotics. *The Lancet*. 378:369 – 371.
4. Clavenna A, Bonati M (2011) Differences in antibiotic prescribing in paediatric outpatients. *Archives of Diseases in Childhood*. doi.10.1136/acd.2010.18354.
5. Kwint HM, Van der Linden PD, Roukens MMB, Natsch S (2012) Intensification of antibiotic use within acute care hospitals in the Netherlands. *Journal of Antimicrobial Chemotherapy.* 67: 2283 – 2288.
6. Lee CG, Reveles KR, Attridge RT, Lawson KA, Mansi IA, Lewis II JS, and Frei CR (2014) Outpatient antibiotic use in the United States: 2000 – 2010. *Biomedical Central Medicine*. 12:96 doi: 10.1186//1741-7015-12-96.
7. Van Boeckel TP, Gandra S, Ashok A, Caudron Q, Grenfell B, Levin SA et al. (2014) Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. *Lancet Infectious Disease.* 14: 742 – 750.

8. Desalegn AA (2013) Assessment of drug use patterns using the WHO prescribing indicators at Hawassa University teaching and referral hospital, south Ethiopia: a cross sectional study. *BMC Health Services Research.* 13:170.
9. Kimang'a AN. (2012) A situational analysis of antimicrobial resistance drug in Africa – are we losing the battle? *Ethiopian Journal of Health Sciences*. 22(2): 135 – 143.
10. CDC. Antibiotic resistance threats in the United States. (2013) US Department of Health and Human Services, Centre for Diseases Control and Prevention. Georgia, USA.
11. Goossens H, Ferech M, Vander Stichel R, Elsiever M (2005) Outpatient antibiotic use in Europe and associations with resistance: a cross-national database study. *The Lancet*, 365: 579-587.
12. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD (2010) Effect of antibiotic prescribing in primary care on resistance in individual patients: systemic review and meta-analysis. *British Medical Journal.* 340:c2096.
13. Vaccheri A, Silvani MC, Bersalgia L, Motola D, Strahinja P, Vargui A, Poluzzi E, and Montanaro, N. (2008) A 3-year survey on the use of antibacterial agents in 5 Italian hospitals. *Journal of Antimicrobial Chemotherapy.* 61:953-958.
14. Shaban RZ, Cruickshank M, Christainsen K (2012) National surveillance and reporting of antimicrobial resistance and antibiotic usage in Australia. Australian Commission on quality and safety in health care. Sydney.
15. Leung E, Weil D, Raviglione M, Nakatani H (2011) Policy package to combat antimicrobial resistance. *Bulletin World Health Organization*. 89: 390 – 392.
16. World Health Organization (2014) Global Action Plan on antimicrobial resistance. Draft for consultation with member states, October 2014. Geneva.

17. PEPFAR/NAMIBIA (2011) Namibia Global Health Initiative 2011-2015/16. Windhoek
18. European Centre for Disease Prevention and Control (2010) Surveillance of antimicrobial consumption in Europe. Stockholm.
19. Zarb P, Borg MA (2011) Consumption of antibiotics within ambulatory care in Malta. *Malta Medical Journal.* 23 (2): 13 -18.
20. Low M, Nitzan O, Bitterman H, Cohen C, Hammerman C, Lieberman N, et al. (2013) Trends in outpatient antibiotic use in Israel during the years 2000 – 2010: setting targets for an intervention. *Infection*. 41: 401 – 407.
21. Kotwani A, Holloway K, (2011) Trends in antibiotic use among outpatients in New Delhi, India. *Biomed Central Infectious Disease.* 11:99. http://www.biomedcentral.com/1471-2334/11/999.
22. Ferech M, Coenen S, Malhorta-Kumar S, Dvorakova K, Hendrickx E, Seutens C, Goossens H (2006) European Surveillance of Antimicrobial Consumption (ESAC): outpatient antibiotic use in Europe. *Journal of Antimicrobial Chemotherapy*, 58:401-407.
23. Verspotten A, Bolokhovets G, Ghazarayan L, Abilova, V, Pyshnik G, Spasojevic T, et al. (2014) Antibiotic use in Eastern Europe: a cross-national database study in coordination with the WHO Regional Office in Europe. *Lancet Infectious Disease,* http://dx.doi.org/10.1016/S1473-3099 (14)70071-14.
24. Dumpis U, Dimina E, Akermanis M, Tirans E, Veide S (2013) Assessment of antibiotic prescribing in Latvian general practitioners. *Biomed Central Family Practice*. 14: 9 – 13.
25. Bartlett J (2011) A call to arms: the imperative for antimicrobial stewardship. *Clinical Infectious Disease*, 53 (S1): S4 – S7.

26. Freire-Moran L, Aronsson B, Manz C, Gyssens IC, So AD, Monnet DL, Carrs O (2011) Critical shortage of new antibiotics in development against multidrug-resistant bacteria – time to react is now. *Drug Resistance Updates.* 14: 118 – 124.

27. Han KSS, Ramsay Y (2013) Surveillance alone plays a key role in curbing the overuse of antimicrobials: the major role of antibiotic stewardship. *South African Medical Journal*. 103 (6): 368.

28. Pendleton JN, Gorman SP, Gilmore BF (2013) Clinical relevance of the ESKAPE pathogens. *Medscape.* 11 (3): 297-308.

29. Campos J, Ferech M, Lazaro E, De Abajo F, Oteo J, Stephens P, Goossens H (2007) Surveillance of outpatient antibiotic consumption in Spain according to sales data and reimbursement data. *Journal of Antimicrobial Chemotherapy.* 60:697-701.

30. Gagliotti C, Mazzetti, Moro ML (2009) Comparison of sales and reimbursement data regarding outpatient antibiotic use in northern Italian region. *Pharmacoepidemiology & Drug Safety*. 18 (11):1115-1118.

31. Essack Y, Schellack N, Pople T, Van der Merwe L (2011) Antibiotic supply chain and management in human health. Global Antibiotic Resistance Partnership – Situational Analysis. Antibiotic use and resistance in South Africa. Part 2. *South African Medical Journal.* 101 (8): 562–566.

Authors' contributions

DDP carried out the data collection, some data analysis and prepared the manuscript. MSL was the supervisor and she carried out the data analysis and helped with writing the manuscript. SYE was the lead in the design of the data extraction tool and analysis tool for the wholesale data and assisted with writing the manuscript. All authors read and approved the final manuscript.

Legends of Tables

Table 1: Top 5 antibiotic consuming towns

Table 2: Antibiotic use by class over the four year period expressed as DDD/1000/day by prescription claims and wholesale data

Table 3: Top 9 highest consumed antibiotics over a 4 year period expressed as DDD/1000/day (DID)

Supplementary table 1: Antibiotic use by gender

Supplementary table 2: Antibiotic use by age group

Supplementary table 3: Antibiotics by dispenser and generic indicator

Supplementary table 4: Top 10 antibiotics and their associated cost

Supplementary Tables:

Tables

Table s1: Antibiotic use by gender

Number of antibiotic prescriptions by gender				
Antibiotics	**Gender**			
Frequency	**F**	**M**	**N**	**Total**
Amikacin	91	122	0	213
Amoxicillin/Clavulanic Acid	127,412	112,688	7	240,107
Amoxycillin	29,892	21,441	1	51,334
Amoxycillin/Flucloxaci	8,824	9,058	0	17,882
Ampicillin	439	430	0	869
Ampicillin/Cloxacillin	4,638	5,064	0	9,702
Azithromycin	46,107	35,855	1	81,963
Benzathine Penicillin	897	1095	0	1,992
Benzyl penicillin	191	180	0	371
Cefaclor	1,463	1,258	0	2,721
Cefadroxil	2,180	1,598	0	3,778
Cefazolin	14	5	0	19
Cefepime	3	1	0	4
Cefotaxime	32	47	0	79
Cefoxitin	19	34	0	53
Cefpirome	401	315	0	716
Cefpodoxime	17,669	16,617	3	34,289
Cefprozil	2,322	2,216	0	4,538
Ceftazidime	3	0	0	3
Ceftriaxone	32,015	29,418	0	61,433
Cefuroxime	96,257	77,468	5	173,730
Cephalexin	2,023	1,937	0	3,960
Cephradine	16	18	0	34
Chloramphenicol	346	244	0	590
Ciprofloxacin	56,141	45,858	0	101,999
Clarithromycin	40,347	34,078	0	74,425
Clindamycin	3,742	3,206	0	6,948
Cloxacillin	3,911	4,087	0	7,998
Doxycycline	19,614	16,655	0	36,269

Ertapenem	37	8	0	45
Erythromycin	10,910	9,275	0	20,185
Flucloxacillin	49	70	0	119
Gemifloxacin	4,948	4,655	0	9,603
Gentamicin	3,789	3,687	0	7,476
Levofloxacin	8,543	5,646	0	14,189
Linezolid	2	3	0	5
Lomefloxacin	294	218	0	512
Loracarbef	6,910	6,452	0	13,362
Lymecycline	45	38	0	83
Meropenem	21	18	0	39
Minocycline	627	410	0	1,037
Moxifloxacin	6,516	5,826	0	12,342
Norfloxacin	4,814	3,156	0	7,970
Ofloxacin	4,082	3,694	0	7,776
Oxytetracycline	169	136	0	305
Penicillin	1,225	809	0	2,034
Piperacillin	4	10	0	14
Procaine penicillin	170	222	0	392
Roxithromycin	592	444	0	1,036
Streptomycin	125	92	0	217
Telithromycin	3,945	3,247	0	7,192
Trimethoprim	49,508	55,760	0	105,268
TOTAL (N)	604,334	524,869	17	1,129,220
PERCENT (%)	53.52	46.48	0	100

$p<0, 0001$
Cramer's $V= 0.205$

Table s2: Antibiotic use by age group

Table of antibiotic use by age group						
Antibiotic	**Age group (n = # of prescriptions)**					
Frequency	**< 12**	**≥12 - ≤18**	**≥ 18 to ≤ 45**	**≥ 45 - ≤ 65**	**> 65**	**Total**
Amikacin	0	3	125	77	8	213
Amoxicillin/Clavulanic	78,700	20,722	84,832	52,182	3,628	240,064
Amoxycillin	12,408	4,451	21,487	12,109	840	51,295
Amoxycillin/Flucloxaci	4,083	1,754	7,455	4,310	279	17,881
Ampicillin	217	59	307	268	18	869
Ampicillin/Cloxacillin	2,405	895	3,881	2,413	106	9,700
Azithromycin	16,067	4,891	37,616	21,784	1,596	81,954
Benzathine penicillin	141	112	1,010	708	21	1,992
Benzyl penicillin	129	20	124	97	1	371
Cefaclor	1,683	188	405	416	29	2,721
Cefadroxil	894	277	1,502	1,064	41	3,778
Cefazolin	0	1	11	6	1	19
Cefepime	0	0	3	1	0	4
Cefotaxime	2	2	31	37	7	79
Cefoxitin	2	2	30	19	0	53
Cefpirome	5	42	451	218	0	716
Cefpodoxime	22,582	3,649	5,163	2,704	181	34,279
Cefprozil	3,298	463	488	273	16	4,538

Ceftazidime	0	0	0	2	1	3
Ceftriaxone	8,354	2,756	28,673	20,422	1,221	61,426
Cefuroxime	46,806	14,504	65,281	43,417	3,692	173,700
Cephalexin	3,412	185	276	80	7	3,960
Cephradine	0	5	18	11	0	34
Chloramphenicol	21	39	255	235	40	590
Ciprofloxacin	897	2,636	56,210	38,329	3,927	101,999
Clarithromycin	16,504	5,114	29,893	21,504	1,407	74,422
Clindamycin	106	436	3,322	2,649	435	6,948
Cloxacillin	485	732	3,807	2,819	155	7,998
Doxycycline	266	1,799	21,136	12,339	728	36,268
Ertapenem	0	0	14	28	3	45
Erythromycin	8,522	2,300	5,599	3,401	348	20,170
Flucloxacillin	11	5	56	43	4	119
Gemifloxacin	13	119	4,736	4,261	474	9,603
Gentamicin	1,691	442	2,809	2,262	272	7,476
Levofloxacin	65	203	7,654	5,657	610	14,189
Linezolid	0	0	2	3	0	5
Lomefloxacin	1	7	259	219	26	512
Loracarbef	6,805	1,315	3,135	2,017	90	13,362
Lymecycline	0	21	38	20	4	83
Meropenem	0	1	20	13	5	39

Minocycline	8	91	699	225	14	1,037
Moxifloxacin	133	232	5,308	5,699	970	12,342
Norfloxacin	40	154	4,275	3,045	456	7,970
Ofloxacin	22	105	4,176	3,241	232	7,776
Oxytetracycline	1	46	168	83	7	305
Penicillin	376	491	724	419	24	2,034
Piperacillin	0	0	4	6	4	14
Procaine penicillin	118	42	154	74	4	392
Roxithromycin	7	45	481	464	39	1,036
Streptomycin	0	18	116	80	3	217
Telithromycin	20	202	3,649	3,085	236	7,192
Trimethoprim	15,024	3,612	40,800	44,743	1,082	105,261
TOTAL (N)	252,324	75,188	458,668	319,581	23,292	1,129,053
PERCENT (%)	22	7	41	28	2	100

$p<0.0001$
Cramer's $V = 0.0424$

Table s3: Antibiotics by dispenser and generic indicator

Antibiotic use by dispenser		
Dispenser	Frequency	Percent
Doctor	516,780	45%
Pharmacist	612,440	54%
Total	1,129,220	100

Antibiotics dispensed as generic by dispenser			
Frequency	Antibiotic prescription a generic		
Dispenser	N	Y	Total
Doctor	117,043	392,972	510,015
Pharmacist	140,384	466,845	607,229
Total (N)	257,427	859,817	1,117,244
Percent (%)	23.05	76.96	100

$p < 0.0001$
Cramer's $V = 0.1093$

Table s4: Top 10 antibiotics and their associated cost

Total AB cost per year	2008 (N= R26,941,120)		2009 (N = R33,423,266)		2010 (N= R36,651,164)		2011 (N= R43,711,348)	
Antibiotic	Cost per antibiotic	% total AB cost	Cost per antibiotic	% total AB cost	Cost per antibiotic	% total AB cost	Cost per antibiotic	% total AB cost
Amoxicillin/Clavulanic acid	R6,386,213	23.70	6,920,556	20.71	R7,144,060	19.49	R9,210,120	21.07
Amoxicillin	R252,666	0.94	R269,922	0.81	R277,172	0.76	R268,151	0.61
Azithromycin	R1,658,627	6.16	R2,854,055	8.54	R3,478,219	9.49	R4,496,379	10.29
Cefpodoxime	R1,306,707	4.85	R1,101,067	3.29	R1,262,629	3.44	R1,250,311	2.86
Ceftriaxone	R1,043,787	3.87	R1,663,353	4.98	R1,607,022	4.38	R1,861,870	4.26
Cefuroxime	R5,728,547	21.26	R7,803,031	23.35	R8,928,472	24.36	R11,816,865	27.03
Ciprofloxacin	R1,200,562	4.46	R1,613,330	4.83	R1,934,721	5.28	R2,115,987	4.84
Clarithromycin	R2,301,450	8.54	R2,469,922	7.39	R3,216,891	8.78	R3,119,778	7.14
Doxycycline	R708,616	2.63	R840,303	2.51	R686,809	1.87	R550,878	1.26
Trimethoprim/Sulfa	R979,800	3.64	R924,622	2.77	R744,401	2.03	R800,654	1.83
TOTAL	R21,566,975	80.05	R26,460,162	79.17	R29,280,396	79.89	R35,490,993	81.19

3.2. Manuscript 2

In this section, the following manuscript titled “Antibiotic use and resistance in the private sector in Namibia” is presented. The paper was submitted for review to **Iranian Journal of Public Health** and prepared in accordance with the *Author Guidelines* of the said journal (provided in Annexure F).

The author guidelines are also available from http://ijph.tums.ac.ir/index.php/ijph/about/submissions#authorGuidelines

The references for this manuscript are provided at the end of this manuscript.

The article has been submitted for review (submission acknowledgement communication is found in Annexure G).

Antibiotic Use and resistance in the private sector in Namibia

Dawn D Pereko[3], B. Pharm, MPH, PhD student, Medicine Usage in South Africa, Faculty of Health Sciences, School of Pharmacy, North-West, University, Potchefstroom, South Africa.

Email: dineopereko@gmail.com

Sabiha Y. Essack[4], B. Pharm, M. Pharm, PhD, Professor, Dean, School of Health Sciences, University of KwaZulu-Natal, Durban, South Africa.

Email: essacks@ukzn.ac.za

Martie S. Lubbe, B. Pharm, M. Pharm, PhD, Professor, Leader, Medicine Usage in South Africa, Faculty of Health Sciences, School of Pharmacy, North-West University, Potchefstroom, South Africa

Email: martie.lubbe@nwu.ac.za

Study design: A retrospective drug utilization research to quantify antibiotic usage in the private sector of Namibia

Running Title: Antibiotic use and resistance

Corresponding author: Dawn D. Pereko

P.O. Box 35209, Windhoek, Namibia

Tel: + 264 61 232873, Fax: +264 61 231273

M: +264 81 249398

dineopereko@gmail.com

---

[3] Corresponding author: Dawn D Pereko, P.O. Box 35209, Windhoek, Namibia Tel: + 264 61 232873, Fax: +264 61 231273; M: +264 81 249398; dineopereko@gmail.com

[4] Member of the Global Respiratory Infection Partnership (GRIP) sponsored by Reckitt and Benckiser

Antibiotic Use and resistance in the private sector in Namibia

Abstract

Background: Antibiotics resistance is a global concern. A considerable body of evidence has shown a direct association between antibiotic use and the development of resistance. The objective of this study was to ascertain susceptibility patterns in the private health sector and determine possible relationship between antibiotic usage and resistance in Namibia.

Methodology: A retrospective analysis of prescription claims data 2008 to 2011 and microbiological reports for 2001 to 2011 was conducted. Antibiotic use was expressed in defined daily dose per 1000 inhabitants per day in accordance with the anatomical therapeutic classification. Antibiotic resistance was expressed as sensitivity rates.

Results: Antibiotic consumption was high (27DDD/1000/day) and increased by 3.5% between 2008 and 2011. Beta- lactams were the highest used antibiotic class followed by macrolides. Antibiotic resistance showed very little change between 2010 and 2011. Overall, the greatest resistance was observed with chloramphenicol (18%). *E. coli* and *S. aureus* showed great resistance to amoxicillin (23% and 7 % respectively). Overall, increasing resistance was observed in older antibiotic agents as compared with the newer agents. No association between antibiotic use and resistance was observed however statistical significance increased when correlating earlier antibiotic use with resistance of later years.

Conclusion: Antibiotic resistance profiles observed in this study are comparable to those in other African countries. The study could not establish a statistically significant correlation between antibiotic use and resistance. Continuous monitoring of antibiotic use and resistance in Namibia in the context of the WHO Global Action Plan is recommended.

Key words: antibiotics, antibiotic use, antibiotic resistance, Namibia

Introduction

Antibiotic resistance is a major public health problem globally with both clinical and financial consequences (1-3). The European Commission estimates 250,000 deaths and cost of over 1,5 billion Euro due to antimicrobial resistance each year (4). The Unites States on the other hand reports that two million people daily are infected with antibiotic resistant bacteria and at least 23,000 of these die (5). Though there are no statistics in Africa, antibiotic resistance has been described as a growing problem that accounts for most of Africa's disease burden (6 -8). The WHO also reports that despite the limited availability of data, the African region shows worldwide trends of increasing antibiotic resistance (9).

Resistance is a result of antibiotic selection pressure as a result of antibiotic overuse, under-use of irrational or indiscriminate use (5, 10, 11). In 1998, Finch suggested that antibiotic resistance is a function of time and use (12). Since then, numerous studies have been conducted that show the relationship between antibiotic use and the development of resistance over time (13 – 15).

Knowledge of local sensitivity patterns is important in guiding optimal empiric treatment and rational use of antibiotics. These can be effectively monitored through the use of antibiograms (16 – 18). In Namibia, a few studies were done to look into the sensitivity patterns of antimicrobials. However, these were done only in the public sector and do not look into the correlation of use and resistance pattern.

A combined strategy of surveillance for antibiotics, that is using both consumption and resistance data, provides a better understanding of the relationship between usage and resistance (19). Accordingly, the objective of this study was to ascertain susceptibility patterns in the private health care setting and determine possible relationship between antibiotic use and resistance in Namibia.

Methodology

Ethical clearance for this study was obtained from the Research Ethics Committee (Human), Faculty of Health Sciences, North-West University (Ethical clearance number NWU-00028-13-s1). All analyses were conducted on anonymized, aggregated records therefore no individual patient consent was necessary. Additional permission was obtained from the medical aid administrators and the specific laboratory.

Antibiograms: antibiotic sensitivity data

Antibiograms for pathogens isolates were provided by the laboratory for the period 2001 to 2011.

Viable specimens were processed in accordance with in-house procedures. Methodology for pathogen identification was dependent on the source of the specimen, for example, uri-select is used for urine samples while blood agar and chalk plates were used for cerebrospinal fluid samples (CSF). Sensitivity testing was performed in accordance with the Clinical Laboratories Standard Institutions (CLSI) guidelines. The first line test for sensitivity testing is the Kirby-Bauer disk diffusion method whereby the discs containing antibiotics were placed over an agar plate inoculated with the organism. The size of the zone of inhibition was equated with whether or not the organism was sensitive or resistant to the antibiotic at standard doses. Antibiotic susceptibilities were then reported in qualitative recorded and entered onto Meditech® and stored by organism. Annual sensitivity reports were then drawn from these data.

From the antibiograms, the number of isolates tested and those testing susceptible were computed. Percentage susceptibility for each antibiotic was calculated by combining all species for which the antibiotic was indicated. The nature of the information provided did not allow for identification of information by source of specimen.

Antibiotic use data

Antibiotic use data covering a four (4) year period from 01 January 2008 to 31 December 2011 were collected from the medical aid claims data of a medical aid fund that covers 54% of the insured population. Only data related to antibiotics for systemic use (anatomical therapeutic classification (ACT) J01) were collected and analysed using the defined daily dosage (DDD) methodology. The ACT/DDD methodology was used to evaluate the consumption of antibiotics and each antibiotic was assigned a DDD obtained from the ACT/DDD index 2013 (www.whocc.no/act_ddd_index). The data were expressed as DDD/1000 population/day using the formula:

DDD/1000/day = (Total consumption in DDDs/Total population covered x Total days in the period of data collection) x 1000.

Statistical analysis

Microsoft Excel 2010 and SAS Version 9.1.3 (SAS Institute, Cary, NC) were used for analysis. Descriptive statistics were used to summarize frequencies and distribution of microbial isolates and their sensitivity to different antibiotics. All statistical significance was considered with probability of $p < 0.05$. The practical significance of the results was computed when the *p*-value was statistically significant ($p \leq 0.05$). Chi-square test ($\chi 2$) was used to determine if an

association exists between proportions of two or more groups, The Cramer's *V* statistics was used to test practical significance of this association. Because of the non-linear nature of the data, Spearman's correlation coefficient was used to determine the relationship between antibiotic use and sensitivity.

Results

Antibiotic consumption

Overall antibiotic use measured in DDD/1000 population per day (DID) was high (27) and showed a 3.5% increase between 2008 and 2011. Most frequently used antibiotic class was beta-lactams followed by macrolides. The most frequently used antibiotic over the years was amoxicillin with clavulanic acid. A high increase in antibiotic use over the 4 year period was observed for macrolides especially clarithromycin and azithromycin. Table 1 shows antibiotic usage (including changes in usage over the 4 years) by pharmacological group.

Table 1: Trends in antibiotic use by class expressed in DDD/1000/day

Antibiotic Class	ATC	2008	2009	2010	2011	Diff	% Diff
Penicillin	J01C	13.64	10.44	9.53	10.22	-3.4	-25.07
Cephalosporin	J01D	4.5	4.7	5.2	6.3	1.8	40.00
Macrolides	J01F	1.97	4.65	5.09	5.67	3.7	187.82
Quinolones	J01M	2.6	2.6	2.7	2.8	0.2	7.69
Aminoglycosides	J01G	0.106	0.073	0.57	0.078	0.0	-26.42
Tetracyclines	J01A	2.3	2.1	1.8	3.4	1.1	47.83
Other	J01X	0.056	0.068	0.127	0.088	0.0	57.14
Other Beta Lactams		0.47	0.77	0.71	0.04	-0.4	-91.49

*ATC denotes the anatomic therapeutic classification of the WHO

Antibiotic resistance

Because of the gap in data between 2005 and 2010, only sensitivity data for 2010 and 2011 were used to allow for comparability with antibiotic usage data year on year from 2008 to 20011. A total of 3506 and 5037 isolates were reported for 2010 and 2011 respectively. Nine species were reported and *Escherichia coli* was the most commonly isolated organism (49%) followed by *Staphylococcus aureus* (16 %). The other isolates reported were *Enterococcus* spp. (14%), *Streptococcus pyogenes (2.7%)*, *Haemophilus influenza (3.03%*), *Pseudomonas aeruginosa (8.45%)*, *Salmonella* spp. (3.57%) and *Shigella* spp. (1.09%).

Escherichia coli showed resistance to amoxicillin and co-trimoxazole. Decreasing sensitivity to amoxicillin/clavulanic acid and nalidixic acid by *E. coli* was also observed.

S. aureus showed the highest resistant of all the pathogens to amoxicillin.

S. pneumonia showed sensitivity to amoxicillin and 3rd generation cephalosporins. Decreased sensitivity to erythromycin and tetracycline was observed.

S. pyogenes showed sensitivity to all antibiotics tested and reduced sensitivity to tetracycline (84%). Not much change in sensitivity. *Heamophilus spp.* species showed sensitivity to all antibiotics except co-tromixazole.

With regards to stool pathogens, *Shigella* spp. is resistant to ampicillin/amoxicillin, cotrimoxazole and chloramphenicol; while *Salmonella* spp. showed resistance to chloramphenicol and reduced sensitivity to cotrimoxazole and ampicillin.

Resistance between 2010 and 2011 for individual antibiotics for different isolates remained fairly stable. The table below shows percentage susceptibility of each antibiotic calculated by combining all species for which the antibiotic is indicated.

Table 2: Percentage antibiotic sensitivity for all isolates

Antibiotic	2001	2002	2003	2004	2005	2010	2011
Ampicillin	67.62	69.37	65.62	64.25	65.5	62	61.88
Augmentin	95	96	93	92	93.5	88.33	88.33
Cloxacillin	95	95	95	93	96	89	92
Cotrimoxazole	54.8	56.8	56.16	47.83	43.33	52	53.4
Cephalosporins 2nd	99	99	98.5	98.5	97.5	88.5	91.67
Cephalosporins 3rd	99.2	98.2	98.8	99.4	95.8	95.57	96
Cephalosporins 4th	0	0	0	0	0	86.5	87.5
Gentamycin	97.5	96.5	93.5	94.5	90.5	76.75	82.5
Nalidixic Acid	97	93	83	85	85.5	84	82.83
Nitrofurantoin	91.5	99	97	92.5	96.5	96	97.5
Ofloxacin	96.8	99.4	98	95.8	95.8	95.5	92.5
Ciprofloxacin	99	98.4	98.2	97.4	96.2	89.86	89.86
Moxifloxacin	0	0	0	0	0	96.67	99.33
Erythromycin	91.25	90.5	89.5	85.5	86.5	86	83.67
Azithromycin	0	0	0	0	0	100	100
Tetracycline	87	90.5	92.5	88	86.25	66.75	84.5
Clindamycin	74.5	93.5	91.5	95	90	43.5	81.5
Fucidic acid	95	98	97	95	98	93	96
Chloramphenicol	76	50	71	63	74.5	18	18

Chloramphenicol showed the lowest sensitivity profile. A modest rise in resistance to ciprofloxacin, gentamycin, nalidixic acid and chloramphenicol over the 11 year period (2001 – 2011) was observed.

Comparing antibiotic use and resistance pairs for 2010 and 2011 respectively showed no association between antibiotic usage and resistance both at individual antibiotic level and at antibiotic class level.

Comparing earlier antibiotic use (2008) with later resistance (2010 and 2011 respectively) still showed no correlation but the p value decreased from $p = 0.856$ in 2010 to $p = 0.056$ in 2011. Same trends were seen when comparing antibiotic use in 2009 and 2010 with sensitivity data of 2010 and 2011 as seen on table 3 below.

Table 3: Comparing changes in significance of earlier antibiotic use with resistance in later years (*p* value)

	Antibiotic use year		
Sensitivity year	2008	2009	2010
2010	0.856	0.858	0.843
2011	0.056	0.058	0.153

Comparing earlier antibiotic use with resistance in later years shows a trend in decreasing *p*-value that is approaching significance ($p<0.05$).

Discussion

This study reports on observed antibiotic resistance patterns in the private sector of Namibia and the association between these patterns and antibiotic use. Antibiotic use in Namibia is high and logically, an association is expected between such usage and resistance (13, 20).

Over the 4 year period, an overall increasing trend in antibiotic use was observed. Generally, a decrease in beta-lactams was observed and an increase in the use on macrolides was observed over the 4 year period. On the other hand, despite the gap in data between 2005 and 2010 (when analysis was not recorded and reported), antibiotic resistance showed very little change between 2001 and 2011. This was observed across all organisms and all antibiotics. However increasing resistance has been observed in older antibiotic agents as compared with the newer agents.

Sensitivity profiles observed in the private sector of Namibia are similar to those reported elsewhere in Africa. Sensitivity profiles similar to those reported for *E. coli* were reported in Ethiopia and Ghana (21,22) and also in the Namibia public sector (23). Similarly, sensitivity profiles similar to *S. aureus* were reported in Gabon, Ethiopia and other Sub-Saharan countries (22, 24, 25). Decreased sensitivity to erythromycin and tetracycline by *S. pneumonia* was observed in South Africa (25).

When antibiotic use and prevalence of resistance were compared, no statistically significant correlation was found both at individual antibiotic level and at the level of the antibiotic class. However, comparing earlier antibiotic use (2008) with prevalence of resistance in later years

(2010 and 2011), a decreasing trend in *p*-value was year on year, with the trend approaching significance. Correlating earlier antibiotic use with later resistance also showed that as the volume of antibiotic consumption increases, the time to reach the same strength of correlation is shorter. For example, in 2009 and 2010, the volume of antibiotics used were higher and the corresponding resistance a year later showed a lower p-value compared to earlier p-value. This shows that increasing the volume of antibiotic consumption increases the selection pressure for the development of resistance (26,27,28). This finding suggests that resistance is a function of time and antibiotic use, findings that were previously reported by others (29,30,31). This implies that prior antibiotic exposure can have an impact in future resistance

The relationship between antibiotic use and resistance is complex. The lack of correlation between antibiotic use and resistance has not only been found in this study but has been reported by others and attests to the complex relationship between the two (1, 14, 32, 33). This has been attributed to confounding factors such as infection control, sample selection bias, susceptibility testing methods and patient's underlying illness.

Other methodological factors that have been cited as possible contributors to the lack of correlation between antibiotic use and resistance the fact that data used were aggregated data. Resistance selection pressure occurs at an individual level and DDD does not measure individual exposure (14,33,34. In 2005, Hay *et al.,* (32) concluded that "associations at individual level were obscured by analysis of aggregate data".

There are several limitations to this study. Firstly, the laboratory data was only available for two years and could therefore not allow for 4 year comparison with the usage data. Secondly, aggregate data was used and as pointed out already, this could potentially obscure the associations that could be present at individual level. Thirdly, it is unlikely that every infection seen in the private sector actually engendered a sample for microbiological analysis. Finally, the laboratory serves a much smaller population as compared to the rest of the country therefore the sensitivity results do not show the full picture of the country. All these suggest that the sensitivity data presented here could be an under-estimation of the actual sensitivity in the private sector. Equally, use data represent only a small fraction of the population (those accessing care in the private sector) and not a full picture of antibiotic usage in a country with dual health care system.

Conclusion

Understanding the relationship between antibiotic use and the prevalence of resistance is crucial to the fight against antimicrobial resistance. This was the first study in Namibia to ascertain

susceptibility patterns in the private health sector and determine possible relationships between antibiotic use and resistance.

The study found an increasing trend in use of antibiotics especially broad spectrum antibiotics. While resistance trend remained stable over the observed period, greater resistance to older agents was observed. The study also found that while there was no obvious correlation between antibiotic use and resistance, trends showed that prior antibiotic use as well as the volume of antibiotics had a bearing on sensitivity in later years.

In line with the objectives 2 and 4 of the WHO Global Action Plan, a surveillance system should be established that will routinely monitor sensitivity profiles of common organisms from health care facilities and communities. This should be linked to monitoring of antibiotic consumption and together these data should be used to promote responsible use of antibiotics in order to extend their lifespan. Such a system should collect data from both the public and private health sectors.The results of this study and the methodology employed therefore could serve as a starting point (35).

Results of this surveillance should be shared with all health professionals and should be shared at regional and global fora.

Acknowledgements

The authors would like to thank the staff and management of the laboratory that provided the data specifically Dr Braam van Greunen and Mr Advance Manghonzo for their advice and support. The authors also wish to acknowledge the medical aid fund and administrators who provided the prescription claims data.

References

1. Essack, S.Y., Connoly, C. & Sturm, S.W. (2005). Antibiotic use and resistance in public sector hospitals in KwaZulu-Natal. *South African Medical Journal*, 95 (11): 865 – 870.
2. Shaban, R.Z., Cruickshank, M., Christainsen, K. (2012). National surveillance and reporting of antimicrobial resistance and antibiotic usage in Australia. Australian Commission on quality and safety in health care. Sydney.
3. van Bijnen, Evelien M.E., den Heijer, CDJ., Paget, J., Stobberingh, E.E., Verheij, R.A., Bruggeman, C.A., Pringle, M., Goossens, H., Schellevis, F.G. (2011). The appropriateness of prescribing antibiotics in the community in Europe: study design. *BMC Infectious Diseases*, 11:293- 297.
4. European Commission. (2013). Antimicrobial resistance policy document. http://ec.europa.eu/health/antimicrobial_resistance/policy/index_en.htm .
5. Centre for Disease Control and Prevention (CDC). (2013). Antibiotic resistance threats in the United States. US Department of Health and Human Services, Centre for Diseases Control and Prevention. Georgia, USA.
6. Kimang'a, A.N. (2012). A situational analysis of antimicrobial drug resistance in Africa: are we losing the battle? *Ethiopian Journal of Health Sciences* 22(2):135 – 143.
7. Lancet Infectious Disease Commission. (2013). Antibiotic resistance – the need for global solutions. *The Lancet* S1473-3099 (13)70318-9.
8. Okeke I.N., Aboderin, O.A., Byarugaba, D.K., Ojo., K , Opniten, J. (2007). Growing problem of multi-drug resistant enteric pathogens in Africa. *Emerging Infectious Diseases,* 13 (11): 1640 – 1646.
9. WHO. (2014). Antimicrobial resistance: global report on surveillance. World Health Organization, Geneva, Switzerland.
10. Byarugaba, D. K. (2004). A view of antimicrobial resistance in developing countries and responsible risk factors. *International Journal of Antimicrobial Agents*, 24: 105- 110.
11. Kotwani, A., Holloway, K., Chaudhury, R.R. (2009). Methodology for surveillance of antimicrobial use among outpatient in Delhi. *Indian Journal of Medical Research*, 129: 555 – 560.
12. Finch, R.G. (1998). Antibiotic resistance. *Journal of Agntimicrobial Chemotherapy* 42:125 – 128.
13. Bergman, M., Huikko, S., Huwinen, P. Paakkari, P., Seppala, H. (2006). Macrolides and azithromycin use are linked to increased macrolide resistance in *Streptococcus pneumoniae*. *Antimicrobial Agents and Chemotherapy* 50 (11): 3646 – 3650.

14. Hsu, L., Tan, T., Tam, V., Kwa, A. Fisher, D., Koh, T. (2010). Surveillance and correlation of antibiotic prescription and resistance of gram-negative bacteria in Singaporean hospitals. *Antimicrobial Agents and Chemotherapy* 54 (3): 1173 – 1178.
15. Vernaz, N., Huttner, B., Muscionizo, D., Salomon, J., Bonnabry, P., Lopez-Lozano, J.M., Beyaert, A., Schrenzekl, J., Harbatrth S. (2011). Modeling the impact of antibiotic use on antibiotic-resistant *Escherichia coli* using population-based data from a large hospital and its surrounding community. *Journal of Antimicrobial Chemotherapy*, 69:928 – 935.
16. Orsi, G.B., Falcone, M., Venditti, M. (2011). Surveillance of management of multidrug resistant microorganisms. Medscape. http://www.medscape.com/viewarticle/754322 .
17. Stein, C., Weber, D., Kelley, M. (2003). Using hospital antibiogram data to assess regional pneumococcal resistance to antibiotics. *Emerging Infectious Diseases* 9 (12):211 – 216.
18. Van Beneden, C., Lexau., C., Baughman, W., Barnes, B., Bennett, N., Cassidy, M., Pass, M., Gelling, L., Barret, N., Zell, E., Whitney, C. (2003). Aggregated antibiograms and monitoring of drug-resistant *Streptococcus pneumoniae*. *Emerging Infectious Diseases* 9 (9): 1089 – 1095.
19. World Health Organization (WHO). (2012). The evolving threat on antimicrobial resistance: options for action. Geneva.
20. Hsueh, P., Chen, W. , Luh, K. (2005). Relationship between antimicrobial use and antimicrobial resistance in gram-negative bacteria causing nosocomial infections from 1991 – 2003 at a university hospital in Taiwan. *International Journal of Antimicrobial Agents* 26:463 – 472.
21. Ameko, E., Achio, S. , Alhassan, S. (2012). Effects of self-medication on the efficacy of four antibiotics commonly used in Ghana on clinically isolated micro-organisms. *International Journal of Pure and Applied Sciences and Technology*, 10 (2): 62 – 70.
22. Tirunneh, M., Yifru, S., Gizachew, M., Molla, K., Bolthun, Y., Moges, F., Endris, M. (2014). Changing trends in prevalence and antibiotic resistance of uropathogens in patients attending Gondar University Hospital, Northwest Ethiopia. *International Journal of Bacteriology,* 2014: 1 -7 http://dx.doi.org/10.1155/2014/629424.

23. Mengistu, A. (2014). A review of empirical treatment of urinary tract infections based on national antimicrobial sensitivity data. *The Namibia Medicines Watch*, 4 (1): 6 – 12.
24. Alabi, A.S., Frielinghouse, L., Kaba, H., Koster, K., Huson, M.A.M., Kahl, B.C., Peters, G., Grobusch, M.P., Issifou, S., Kremnser, P.G., Schaumburg, F. (2013). Retrospective analysis of antimicrobial resistance and bacterial spectrum of infection in Gabon, Central Africa. *BMC Infectious Diseases*, 13:455 – 460.
25. Ashley E.A., Lubell, Y., White, N.J, Turner, P. (2011). Antimicrobial susceptibility of bacterial isolates from community acquired infections in Sub-Sahara and Asian low and middle income countries. *Tropical Medicine and International Health*, 16 (9): 1167 – 1179.

26. Bell B.G., Schellevis, F., Stobberingh, E., Goossens, H. , Pringle, M. (2014). A systemic review and meta-analysis on the effects of antibiotic consumption on antibiotic resistance. *Biomed Central Infectious Diseases* 14:13.
27. Costelloe, C., Metcalfe, C., Lovering., A., Mant, D. , Hay, A.D. (2010). Effect of antiniotic prescribing in primary care on antimicrobial resistance in individual patients: systemic review and meta-analysis. *British Medical Journal* 340:c2096.
28. Goosens, H., Ferech, M., Vander Stichel, R. and Elsiever, M. (2005). Outpatient antibiotic use in Europe and associations with resistance: a cross-national database study. *The Lancet* 365: 579-587.
29. Gallini, A., Degris, E., Desplas, M., Bourrel, R. Archambaud, M., Montastruc, J., Lapyere-Mestre, M., Sommet, A. (2010). Influence of fluoroquinolone consumption in inpatients and outpatients on ciprofloxacin-resistant *Escherichia coli* in a university hospital. *Journal of Antimicrobial Chemotherapy* 65: 2650 – 2657.
30. Kritsotakis, E.I., Christidou, A., Roumbelaki, M., Tselentis, Y. , Gikas, A. (2008). The dynamic relationship between antibiotic use and the incidence of vancomycin-resistant Enterococcus: time series modelling of 7 years surveillance data in a tertiary care hospital. *Clinical Microbiology and Infection* 14:747 -754.
31. Mahamat, A., Lavigne, J.P., Fabbro-Peray, P., Kinowski, J.M., Duaress, J.P., Sotto, A. (2005). Evolution of fluoroquinolone resistance among Eschericia coli urinary tract isolates from a French university hospital: application of the dynamic regression model. *Clinical Microbiology and Infection*, 11:301 – 306.
32. Hay, A.D., Thomas, M., Montgomery, A., Wetherell, M., Lovering, A., McNulty, C., Lewis, D., Carron, B., Henderson, E , McGowan, A. (2005). The relationship between primary care antibiotic prescribing and bacterial resistance in adults in the community: a controlled observational study using inpatient data. *Journal of Antimicrobial Chemotherapy*, 56:143 – 156.
33. Lai, C., Wang, C., Chu, C., Tan, C, Lu, C., Lee, Y., Huang, Y., Lee, P , Hsueh, P. (2011). Correlation between antibiotic use and resistance of gram-negative bacteria causing healthcare-associated infections at a university hospital in Taiwan from 2000 – 2009. *Journal of Antimicrobial Chemotherapy*, 66: 1374 – 1382.
34. Schechner, V., Temkin, E., Harbarth, S., Carmeli, Y. , Schwaber, M. (2013). Epidemioloical interpretation of studies examining the effect of antibiotic use on resistance. *Clinical Microbiology Reviews*, 26 (2): 289 – 307.
35. WHO (2014). Global Action Plan on antimicrobial resistance. Draft for consultation with member states, October 2014. Geneva.

3.3. Manuscript 3

In this section, the following manuscript titled “Public knowledge, attitudes and behaviour towards antibiotic usage in Windhoek, Namibia” is presented. The paper was submitted to **Southern African Journal of Infectious Diseases** and prepared in accordance with the *Author Guidelines* of the said journal (provided in Annexure F).

The author guidelines are also available from www.sajei.co.za

The references for this manuscript are provided at the end of this manuscript as well as at the end of the thesis.

The manuscript has been accepted for publication and is scheduled for publication in December 2015 (communication from the editor is found in Annexure G).

Public knowledge, attitudes and behaviour towards antibiotic usage in Namibia

Dawn D Pereko[a5], Martie S. Lubbe[a], Sabiha Y. Essack[b6]

[a]Medicine Usage in South Africa, Faculty of Health Sciences, School of Pharmacy, North-West University, Potchefstroom, South Africa

[b] School of Health Sciences, University of KwaZulu-Natal, Durban, South Africa.

Running head: **Antibiotic use and behaviour in Namibia**

Corresponding author: Dawn D. Pereko

P.O. Box 35209, Windhoek, Namibia

Tel: + 264 61 232873, Fax: +264 61 231273

M: +264 81 249398
dineopereko@gmail.com

Word counts: abstract 245 words; article 3500 words

[5] Corresponding author: Dawn D Pereko, P.O. Box 35209, Windhoek, Namibia Tel: + 264 61 232873, Fax: +264 61 231273; M: +264 81 249398; dineopereko@gmail.com

[6] Member of the Global Respiratory Infection Partnership (GRIP) sponsored by Reckitt and Benckiser

Abstract

Background: The development of antibiotic resistance is a globally recognised human health threat. Overuse of antibiotics is a major contributory factor to the development of resistance. As end users, the public play a role in antibiotic use and the development and spread of resistance. The purpose of the study was to assess the knowledge, attitudes and behaviour of the general population of Namibia accessing care in the private sector regarding antibiotic use.

Methodology: A cross-sectional survey based on self-administered questionnaire was distributed to 600 patients through pharmacies in Windhoek, Namibia. The survey was conducted from March to June 2013.

Results: A total of 446 completed questionnaires were collected. 80% of respondents reported to have used antibiotics in the past year mainly for colds and flu symptoms. The majority of respondents obtained antibiotics through a valid doctor's prescription. A prevalence of 15% of self-medication with antibiotics mainly obtained from pharmacies without a prescription was reported. 80% of respondents reported to complete the antibiotic course. Gaps in population understanding of antibiotics were observed. 64% of the respondents thought that antibiotics were effective against viruses with just less than half admitting that they should take an antibiotic for a cold. 72% of respondents understood that unnecessary use of antibiotics makes them ineffective.

Conclusion: Our study shows sale of antibiotics without a prescription, over prescribing of antibiotic for self-limiting upper respiratory tract infections and gaps in general population knowledge of and attitudes and behaviour towards antibiotics and their use.

Key words: antibiotic use, resistance, self-medication, knowledge, attitudes, Namibia

Introduction

Since their discovery, antibiotics have been hailed as one of the most important discoveries in medical history.[1] Antibiotics have been used successfully to treat infections for the past seventy years, have made the management of infectious diseases easier and contributed to decreased morbidity and mortality due to infectious disease. [2]

However, globally the gains achieved through antibiotics are threatened by the development of antimicrobial resistance (AMR) in both hospital and community settings, [3, 4] making standard treatment ineffective, complicating patient management and increasing patient morbidity and mortality. [5, 6] The development of resistance is associated with high antibiotic usage, [7] particularly inappropriate use. [8] It is exacerbated by social factors including misconceptions about antibiotics, views on infectious diseases; inappropriate prescribing and use, patient demand, self-medication and non-compliance also play a significant role in the development of resistance to antibiotics. [9]

It is therefore important to determine what the community understands about antibiotics and how they use them. However, population based studies on knowledge and attitudes concerning antibiotics are few [10] and those that have been conducted found limited public knowledge and understanding of antibiotics and their usage. In Namibia, no such study has been done. The objective of this study is to determine the knowledge, attitudes and behaviour of the general Namibian population accessing care in the private sector, regarding antibiotic use.

Methods

Ethical considerations

Ethical clearance for this study was provided by the North-West University Research and Human Ethics Committee (Ethical clearance number NWU-00028-13-s1). Additionally, only pharmacies that were willing to participate were included in the study. The study was anonymous to ensure confidentiality.

Study design

This was a cross-sectional community based study conducted between 1 March and 30 June 2013 in Windhoek through a self-administered questionnaire that was distributed through randomly selected private pharmacies. Twenty pharmacies were selected and requested to collect 30 surveys. The questionnaire was divided into two sections – demographic information and knowledge of and attitudes towards antibiotics. The study sample was 600 of whom 446 respondents above 18 years of age comprised the final sample size.

Data analysis

Statistical analysis was performed in SAS Version 9.1.3 (SAS Institute, Cary, NC). All statistical significance was considered with probability of $p < 0.05$. The practical significance of the results was computed when the *p*-value was statistically significant ($p \leq 0.05$). Variables (age, gender, education level, and employment) were expressed using descriptive statistics such as frequencies (n) and percentages (%). Chi-square test ($\chi 2$) was used to determine if an association exists between proportions of two or more groups, The Cramer's *V* statistics was used to test practical significance of this association.

Results

The survey was completed by 446 of the targeted 600 respondents. In terms of demographic characteristics, age groups stratified as $\leq$ 24 years, 25-30 years, 31-38 years and > 38 years were almost equally represented. A greater number of respondents were female (66.14%, n=446), employed (85.48%, n=427), on medical aid (76.76%, n=439) and educated beyond grade 12 (54.71%, n=435). Approximately eighty percent (80.36%, n= 438) had used antibiotics in the past 12 months.

Antibiotic usage was statistically significantly higher among the respondents whose education level was greater than grade 10 ($p = 0.009$, Cramer's $V = 0.1394$). The majority of respondents (85%) received their antibiotics through a doctor's prescription although self -medication was prevalent at 15.47%, the majority of whom obtained them through the pharmacy evidencing a

contravention of pharmacy regulations. Significantly higher numbers of males (64%) (p<0.0001; Cramer's V =0.2072) and people with medical aid (61.82%, p=0.030, Cramer's V = 0.1254) obtained antibiotics without a prescription.

Fifty six percent (56%) of respondents (more females than males) used of antibiotics for colds and flu. Colds and flu symptoms included sore throat (15%), cough (12%) and fever (14%). Thirty-two percent (32%) of participants reported the diagnosis of upper respiratory tract infections (URTI) while 45% reported a diagnosis of "unspecified" infection as the reason given by their doctor for use of antibiotics. Only 14% of respondents (largely male < 25 years old), requested antibiotic from their doctor. Eighty percent (80%) of the respondents reported completing the course while the rest stopped taking antibiotics because they felt better.

The respondents had to answer 5 questions related to knowledge and behaviour concerning antibiotic use. Tables 1 and 2 below present the responses as well as the association between responses and respondents' demographics:

Table 1: Knowledge and behaviour regarding antibiotics

Statement	N	True	False
Antibiotics kill viruses (n=419)	419	268 (64%)	15 (36%)
When I have a cold (sore throat, cough, runny/blocked nose, fever), I should always take an antibiotic to feel better (n= 420)	420	174 (41%)	246 (59%)
When I have a cold, I should get an antibiotic to prevent it from getting worse (n= 417)	417	194 (46%)	223 (54%)
When I visit a doctor sick enough with cold, I usually expect an antibiotic (n= 417)	417	183 (44%)	234 (56%)
Unnecessary use of antibiotics makes them ineffective (n=416)	416	301 (72%)	115 (28%)

Table 2: Association of demographic variables with statements

Statement	Gender		Age		Medical Aid		Employment		Education	
	P	*v*	*p*	*v*	*p*	*v*	*p*	*v*	*p*	*v*
Antibiotics kill viruses	0.05	-0.10	0.51	-0.07	0.03	0.13	**0.02**	0.14	0.23	0.10
When I have a cold, I should take antibiotics to get better quicker	0.34	0.05	**0.01**	0.16	0.62	0.05	**0.00**	0.16	**0.01**	0.17
When I have a cold, I should take antibiotics to prevent getting worse	0.23	0.05	**0.03**	0.15	0.05	0.12	0.20	0.09	0.06	0.14
When I visit a doctor sick enough with cold, I usually expect an antibiotic	0.53	0.03	0.36	0.09	0.12	0.10	0.50	0.06	0.08	0.13
Unnecessary use of antibiotics makes them ineffective	0.90	-0.01	0.01	0.16	0.51	0.06	0.36	0.07	0.03	0.15

Age, employment and education was statistically significantly associated with taking antibiotics for colds, in that older participants were more inclined towards antibiotic treatment.

Discussion

This study revealed three areas of concern: the sale of antibiotics without a prescription; prescription of antibiotics especially for self-limiting upper respiratory tract infections; and the limited knowledge and sub-optimal behaviour of general population with regard to antibiotics and their use.

While the majority of participants (85%) reported to use antibiotics obtained through a doctor's prescription, it is concerning that 15% reported to have self-medicated with antibiotics, a common phenomenon in both developed and developing countries with rates ranging from 3% to 75%.[11, 12] Even more concerning is the finding that 82% of all self-medication cases purchased the antibiotic from a pharmacy without a prescription, contrary to Namibian law (Act 13 of 2003) which classifies antibiotics as "prescription only medicines" that cannot be sold without a doctor's prescription.. This practice is not unique to Namibia but is prevalent in many countries.[13] Studies have shown that antibiotic purchases without a prescription were mainly on

the advice of the pharmacist. [14, 15] While not much has been documented on the reasons why pharmacists dispense antibiotics without a prescription, some have suggested patient demand as an influencing factor.[16]

Tighter enforcement of pharmacy laws and regulations together with educating both pharmacists and general population is needed to address the issue of self-medicating with antibiotics. Stricter reimbursement practices should be employed by the medical aid that would discourage patients purchasing antibiotics without a prescription. These could include having the patient pay out of pocket for such antibiotics and not honouring the claim from the pharmacy that issued antibiotics without a prescription.

Between 44% and 49% of respondents in this study agreed with the statements concerning the use of antibiotics for a colds and flu, a well-documented finding [17, 18] evidencing general misconceptions among the public regarding the use of antibiotics for common infections especially respiratory tract infections.[13] These findings are in line with Velden *et al.* who showed that antibiotics in primary care are mainly prescribed for respiratory tract infections which are usually self-limiting and do not require antibiotic treatment.[19]

Two statements were used to assess respondents' knowledge of how antibiotics work. The majority (64%) of the respondents incorrectly agreed with the statement "antibiotics kill viruses". This lack of knowledge on indication of antibiotics is a reported universally reported not unique to Namibia. For instance, studies in Malaysia reported similar finding to Namibia with 67% of their respondents agreeing with the same statement.[20] When discussing the reasons for use of antibiotics we highlighted that the respondents indicated respiratory tract infection symptoms (which are self-limiting and could be viral in nature) as the reason they used antibiotics. These findings can be explained by the fact that most of the respondents think that antibiotics kill viruses therefore they are likely to seek antibiotic therapy for their viral infections. This validates what has been previously reported that that there are misconceptions regarding the role of antibiotics among patients.[19, 21]

Our study did not assess if respondents understood what a virus is. Other authors of similar studies suggested that general population might have confusion with the term virus and may not realize the difference between the terms bacteria and virus.[18] In our study we noted that respondents used the term "infection" when responding to what the doctor diagnosed them with. Given the fact that infections can be viral or bacterial, it is no wonder that patients would not know the difference between viruses and bacteria if only the term "infection" is used. This highlights the importance of health care providers explaining the differences between viral and bacterial infections when communicating with patients. It also highlights the need for the population to be educated on the indications and actions of antibiotics.

The second statement in determining the knowledge of antibiotics used in our study was "unnecessary use of antibiotics makes them ineffective". Encouragingly, 72% of the respondents correctly agreed with the statement. This is similar to what was reported in Nigeria (76%) and higher than what was reported in New Jersey (58%) and Malaysia (59%).[17, 20, 22] Younger respondents (less than 30 years of age) were the ones who showed the least knowledge of the relationship between antibiotic over use and the development of resistance. Similar finding where knowledge of resistance increased with age was reported by Belkina *et al*.[15]
The attitudes of respondents towards antibiotics were assessed by three statements. Just less than half (41%) of the respondents agreed incorrectly that when they have a cold they should take an antibiotic to get better quicker. Again 47% believed that they should take an antibiotic for a cold to prevent it getting worse while 44% expressed that when they visit a doctor sick enough with a cold, they expect an antibiotic. This is in line with the body of evidence that showed respondents agreeing with this statement ranging from 25% to 67%.[8, 17, 16, 20-23] As with other studies, there was an association between age and level of education and incorrectly agreeing with this statement. Younger respondents (less than 24 years) and those with a lower education (less than grade 11) were the ones who displayed this belief.

As could be expected, respondents who believe that antibiotics kill viruses also tend to believe that they should take antibiotics when having a cold so that they can feel better quicker. These also believe that they should take antibiotics when having a cold to prevent getting worse and also reported to expect an antibiotic from a doctor when sick enough with a cold. The converse

was also found true that those respondents who knew that unnecessary use of antibiotics makes them ineffective reported that they should not take an antibiotic to prevent getting worse when they have a cold.

Conclusion

The results of the survey suggest that population based surveys are important in understanding the public's attitude towards antibiotics as such knowledge is important in contributing to efforts to minimize inappropriate use of antibiotics. Understanding the magnitude of the problem and the population groups most affected can help tailor the efforts to improve antibiotic use among the public to the local situation.

Stringent enforcement of pharmacy regulations; continuous professional education for doctors and pharmacists on the consequences of inappropriate antibiotic use; and education of the public specifically to discourage unnecessary use of antibiotics are suggested interventions.

Acknowledgements

The authors wish to acknowledge the participants and the pharmacists who facilitated data collection.

References

1. Cars, O., Hedin, A., Heddini, A. The global need for effective antibiotics – moving towards concerted action. Drug Resistance Update 2011; 14: 68 – 69.

2. Cartlett, J., Callignon, P., Goossens, H., et al. Society's failure to protect antibiotics. Lancet 2011; 378: 369 – 371.

3. Ashley, E.A., Lubell, Y., White, N.J., Turner, P. Antimicrobial susceptibility of bacterial isolates from community acquired infections in Sub-Saharan Africa and Asian low and middle income countries. Tropical Medicine and International Health 2011; 16 (9): 1167 – 1179.

4. World Health Organization (WHO). The evolving threat of antimicrobial resistance – options for action. 2012. Geneva.

5. CDC. Antibiotic resistance threats in the United States. US Department of Health and Human Services, Centre for Diseases Control and Prevention 2013. Georgia, USA.

6. World Economic Forum. Global risks 2013. Geneva.

7. Bell B.G., Schellevis, F., Stobberingh, E., Goossens, H., Pringle, M. A systemic review and meta-analysis on the effects of antibiotic consumption on antibiotic resistance. Biomed Central Infectious Diseases 2014; 14:13.

8. Yah, Y.S., Edrin, Y, O., Odeh, E.N. Patterns of antibiotic usage by adult populations in the city of Benin, Nigeria. Scientific Research and Essay 2008; 3(3):81 -85.

9. Harbarth, S., Samore, M.H. Antimicrobial resistance determinants and future control. Emerging Infectious Diseases 2005; 11(6): 794 – 801.
10. André, M., Vernby, A., Berg, J., Lundborg, C.S. A survey of public knowledge and awareness related to antibiotic use and resistance in Sweden. Journal of Antimicrobial Chemotherapy 2010; 1292 – 1296.

11. Morgan, D.J., Okeke, I.N., Laxminarayan, R., Perenevich, E.N., Weisenberg, S. Non-prescription antimicrobial use worldwide: a systemic review. Lancet Infectious Disease 2011; 11:692 – 701.

12. Ameko, E., Achio, S., Alhassan, S. Effects of self-medication on the efficacy of four antibiotics commonly used in Ghana on clinically isolated micro-organisms.

International Journal of Pure and Applied Sciences and Technology 2012; 10 (2): 62 – 70.

13. Jose, J., Jimmy, B., AlSabahi, S., Al Sabei, A. A study assessing public knowledge, belief and behaviour of antibiotic use in an Omani population. Omani Medical journal 2013; 28 (5): 324 – 330.

14. Sabry, N.A., Ferid, S.F., Dawoud, D.M. 2014. Antibiotic dispensing in Egyptian community pharmacies: an observational study. Research in Social and Administrative Pharmacy 2014; 10:168 – 184.

15. Belkina, T., Al-Warafi, A., Eltom, E. H., Tadjieva, N, Kubena, A., Vlcek, J. Antibiotic use and knowledge in the community of Yemen, Saudi Arabia and Uzbekistan. Journal of Infection in Developing Countries 2014; 8 (4): 424 – 429.

16. Radyowajati, A., Haak, H. Determinants of antibiotic use in developing world. Child health Research Project Special Report 2002; 4 (1): 1 – 39.

17. Auta, A., Banwat, S.B., David, S., Dangiwa, D.A., Ogbole, E., Tor-anyiin, A.J. Antibiotic use in some Nigerian communities: knowledge and attitudes of consumers. Tropical Journal of Pharmaceutical Research 2013; 12 (6): 1087 – 1092.

18. Shehadeh, M., Suiafan, G., Darwish, R. M., Wazaify, M., Zaru. L, Alja'fari, S. Knowledge, attitudes and behaviour regarding antibiotics use and misuse among adults in the community of Jordan. A pilot study. Saudi Pharmaceutical Journal 2012; 20:125 – 133.

19. Van der Velden, A., Duerden, M. G., Bell, J. et al. Prescriber and patient responsibilities in treatment of acute respiratory tract infections – essential for conservation of antibiotics. Antibiotics 2013; 2: 316 – 327.

20. Oh, A. I., Hassali, M.A., Al-Haddad, M. S., Sulaiman, S., Shafie, A.A., Awaisu, A. Public knowledge and attitude towards antibiotic usage: a cross-sectional study among the general public in the state of Penang, Malaysia. The Journal of Infection in Developing Countries 2011; 5(5): 338-347.

21. Suiafan, G. A.R., Shehadeh, M., Darwish, D.A., Al-Ijel, H., Yousef, A. M., Darwish, R.M. A cross-sectional study on knowledge, attitude, behaviour related to antibiotic use and resistance among medical and non-medical university students in Jordan. African Journal of Pharmacy and Pharmacology 2012; 6 (10): 763 – 770.

22. Vanden Eng, J., Marcus, R., Hadler, J, et al. . Consumer attitudes and use of antibiotics. Emerging Infectious Disease 2003; 9 (9): 1128 – 1135.

23. Chen, C., Chen, Y., Hwang, K., et al. . Behaviour, attitudes and knowledge about antibiotic usage among residents of Changhua, Taiwan. Journal of Microbiology, Immunology and Infection 2005; 38: 53 – 59.

3.4. Manuscript 4

In this section, the following manuscript titled "**Antibiotic use in Namibia: prescriber practices for common community infections**" is presented. The paper was prepared according to the specific *Author Guidelines* for the South African Family Practice and submitted for review to the same journal. The Author guidelines are provided in Annexure F.

Author guidelines are also available from www. safpi.co.za.

The article has been accepted and published online http://dx.doi.org/10.1090/20786190.2015.102404021

South African Family Practice
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/ojfp20

Antibiotic use in Namibia: prescriber practices for common community infections

Dawn D Pereko[a], Martie S Lubbe[a] & Sabiha Y Essack[b]
[a] Medicine Usage in South Africa, Faculty of Health Sciences, School of Pharmacy, North-West University, Potchefstroom, South Africa
[b] School of Health Sciences, University of KwaZulu-Natal, Durban, South Africa
Published online: 29 May 2015.

South African Family Practice 2015; 1(1):1–5
http://dx.doi.org/10.1080/20786190.2015.1024021

S Afr Fam Pract
ISSN 2078-6190 EISSN 2078-6204

RESEARCH

Antibiotic use in Namibia: prescriber practices for common community infections

Dawn D Pereko[a]*, Martie S Lubbe[a] and Sabiha Y Essack[b]

[a]*Medicine Usage in South Africa, Faculty of Health Sciences, School of Pharmacy, North-West University, Potchefstroom, South Africa*
[b]*School of Health Sciences, University of KwaZulu-Natal, Durban, South Africa*
**Corresponding author, email: dineopereko@gmail.com*

Background: Despite the threat of resistance, the use of antibiotics globally is high and continues to increase. Much of this use is attributed to overprescribing by physicians. The objective of this study was to assess doctors' management of common community-acquired infections in Namibia.
Methodology: A cross-sectional survey based on a web-based self-administered questionnaire was conducted. Doctors belonging to the local professional associations comprised the study population. Data were collected from March to July 2014.
Results: A 10% (n = 44) response rate was achieved. Respondents were from across the country and practised mainly in the private health sector. Both awareness of local antimicrobial sensitivity rates and ownership of national Standard Treatment Guidelines were poor (20% and 31% respectively). Common practice in managing common infections, with the exception of chronic otitis media, cystitis and pyelonephritis, is to treat empirically. The reported first-line antibiotics of choice were the combination of amoxicillin with clavulanic acid for upper respiratory tract infections and ciprofloxacin for urinary tract infections. Management of infections was the same across all socio-demographic factors and was not influenced by patient workload.
Conclusion: This survey revealed that first-line antibiotic choices of doctors are not informed by the Namibia Standard Treatment Guidelines and the local and regional antimicrobial sensitivity data. Interventions to improve antibiotic prescribing in Namibia should include better dissemination of guidelines and information regarding local antimicrobial sensitivity rates as well as strategies for the implementation of guidelines.

Keywords: antibiotics, antibiotic prescribing, treatment guidelines

Introduction

Antibiotics are pivotal in reducing the burden of infectious disease. Given their effectiveness in fighting infections, their use has become widespread[1–3] and continues to increase. A survey conducted by Princeton University revealed that antibiotic use increased by 36% globally in the past decade (between 2000 and 2010),[4] corroborating the Lancet Infectious Disease Commission Report, which revealed that increased use of antibiotics was observed across all countries regardless of income status[5] with 76% of all increases in antibiotic used globally attributed to the BRICS countries: Brazil, Russia, India, China and South Africa.[4]

High use of antibiotics, especially inappropriate use, is cited as a major driver for the development of resistance. It has further been largely attributed to prescribing practices of physicians.[6–9]Studies have reported that between 20% and 50% of all antibiotic prescriptions are inappropriate.[10–12] Recently, the Lancet Infectious Disease Commission classified prescribers among key players who have the strongest effect on resistance because of their practices.[5]

Given the major role that physicians play in the use of antibiotics, any efforts to decrease the further development of resistance would be advanced if prescribers' practice in prescribing antibiotics were understood. Understanding the attitudes and practices of prescribers can help in determining appropriate interventions to improve antimicrobial stewardship.

Namibia has a dual healthcare system with 82% of the population seeking health care in the public sector and 18% in the private sector. The majority of the health providers, particularly doctors (72%), are practising in the private sector.[13]

The sale of medicines is regulated; antibiotics are scheduled drugs and can therefore only be sold upon prescription by an authorised prescriber.[14] In the public sector medicine prescribing is guided by the Namibia Essential Medicines List (NemList) and the Standard Treatment Guidelines (STGs); medicines are obtained from public facilities and are included in the user fee paid at the point of care.[15] The choice of medicines in the private sector is less regulated.

The objective of this study was to determine the doctors' (general practitioners and specialists) behaviour and clinical practice in prescribing antibiotics in Namibia.

Method

Ethical clearance for this study was obtained from the North-West University Research and Human Ethics Committee (Ethical clearance number NWU-00028-13-s1).

A cross-sectional observational study was conducted between March 11 and July 31, 2014 in Namibia through a web-based self-administered questionnaire that was distributed through the medical professional associations. The study target was 455 doctors (general practitioners and specialists) belonging to the medical associations. To increase response rate, the medical telephone directory was used and doctors were called randomly and asked to participate in the survey. The questionnaire was semi-structured with mainly closed-ended questions and a few open-ended questions designed through extensive literature review of studies with similar objectives and guidance from local experts and subjected to a pilot study. The final questionnaire had 20 questions which surveyed the following items: (i)

demographic data; (ii) workload; (iii) knowledge and possession of treatment guidelines; (iv) knowledge of local sensitivity data; (v) common practice; (vi) strategies for improving antibiotic prescribing.

Data analysis

Data were collected directly on Survey Monkey. Data analysis was performed in SAS Version 9.1.3 (SAS Institute, Cary, NC). All statistical significance was considered with a probability of $p < 0.05$. The practical significance of results was computed when the p-value was statistically significant ($p \leq 0.05$). Descriptive analysis was used to summarise the data and factors associated with doctors' prescribing practices were then evaluated. Variables (age, gender, education level and employment) were expressed using descriptive statistics such as frequencies (n) and percentages (%). A chi-square test (χ^2) was used to determine whether a statistically significant association exists between proportions of two or more groups. Cramer's V statistic was used to test the practical significance of this association (with Cramer's $V \geq 0.5$ defined as practical significance).

Results

Forty-four (44) doctors across the country completed the survey representing a 10% response rate. Majority of the respondents were males (76%), were over the age of 55 years (36%) and were general practitioners (84%). Table 1 gives a summary of the respondents' characteristics.

The respondents were from 12 of the 14 regions of the country with the majority of respondents (57%) from Windhoek, Khomas region. The years in practice of the respondents ranged from 5 years to 44 years with most respondents being in professional practice for 10–30 years.

The majority of respondents (69%) reported not having a copy of the Namibia Standard Treatment Guidelines.

Almost all respondents indicated that they thought that there was a problem with antibiotic usage in the country. The two leading factors for this were indicated as overprescribing by clinicians as well as inappropriate use by patients.

Some 80% of the doctors reported not being aware of the bi-annual aggregate sensitivity data collated by the private laboratory from routinely collected samples obtained from both hospital and ambulatory patients although this is routinely made available to all doctors using the laboratory service.

Treatment of infections

As shown in Figure 1, the common practice in managing common infections, with the exception of chronic otitis media, cystitis and pyelonephritis, is to treat empirically. Only 23% of doctors start treatment after laboratory culture and that is done mainly for chronic sinusitis and nasopharyngitis.

A total of 91% of doctors reported doing laboratory culture when empirical treatment fails. These results were the same across all respondent characteristics.

Choice of antibiotics

For each of the infections mentioned in the preceding section, the doctors were requested to indicate what their usual first choice of antibiotic is. Table 2 shows the respondents' top three antibiotic choices with the first-line antibiotic recommended in the national STGs underlined.

There were no associations between the choice of antibiotic and any of the respondents' characteristics. The practice was the same between those respondents who had guidelines and those who did not.

Monitoring adherence to treatment

Only 36% of doctors reported evaluating antibiotic treatment adherence when seeing a patient for a follow-up visit, while only 12% ($n = 4$) reported having any written material that addressed adherence and compliance with treatment.

Source of information

The main source of information on antibiotics was reported to be the scientific journals (41%), followed by scientific conferences (24%). The pharmaceutical industry was ranked by 38% of

Table 1: Demographic characteristics of respondents

Characteristic	Category	n (%)
Gender	Female	10 (24%)
	Male	32 (76%)
Age	< 35	5 (12%)
	35–45	12 (29%)
	46–55	10 (24%)
	> 55	15 (36%)
Provider type	General practitioner (GP)	36 (84%)
	Specialist	7 (16%)
Sector of practice	Private sector	35 (83%)
	Public sector	2 (5%)
	Both	5 (12%)
Average number of patients per day	< 25	20
	26–50	16
	51–75	5
	> 75	0
Belong to professional association	Yes	37 (90%)
	No	4 (10%)

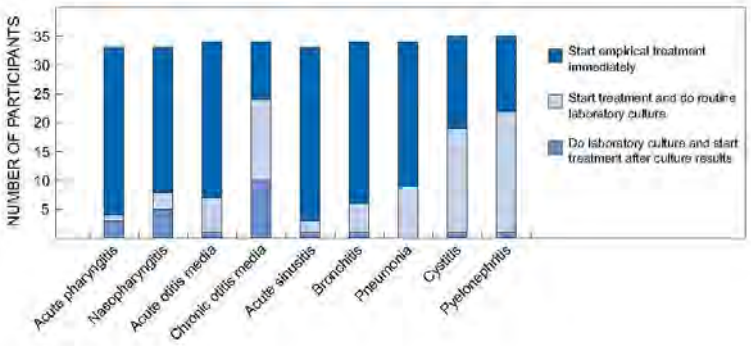

Figure 1: Practice in treating common infections

Table 2: Preferred first choice of antibiotic for different common infections with first-line antibiotics recommended in the national STGs in italics

Infection	First choice of antibiotic (ranked according to # of responses)								
	First	*n*	%	Second	*n*	%	Third	*n*	%
Acute pharyngitis	Amoxicillin	13	44	Amoxicillin/clavulanic acid	5	18	*Penicillin V*	5	18
Nasopharyngitis	Amoxicillin/clavulanic acid	15	35	Amoxicillin	10	26	*Penicillin V*	5	12
Acute otitis media	*Amoxicillin/clavulanic acid*	22	58	Cefuroxime	3	8	Moxifloxacin	3	8
Chronic otitis media	*Amoxicillin/clavulanic acid*	14	38	Cefuroxime	3	8	Moxifloxacin	3	8
Acute sinusitis	*Amoxicillin/clavulanic acid*	10	37	Moxifloxacin	4	15	Azithromycin	4	15
Bronchitis	*Amoxicillin/clavulanic acid*	15	54	Clarithromycin	6	21	Cefuroxime	3	11
Pneumonia	*Amoxicillin/clavulanic acid*	11	36	Ceftriaxone	4	13	Moxifloxacin	3	10
Cystitis	Ciprofloxacin	13	41	*Nitrofurantoin*	4	13	Norfloxacin	4	13
Pyelonephritis	Ciprofloxacin	10	31	*Cefuroxime*	4	13	Amoxicillin/clavulanic acid	3	9

respondents as their second most frequent or priority source of information.

Strategies to improve antibiotic use

The respondents were asked to suggest strategies that could improve prudent use of antibiotics in Namibia. The top 5 strategies suggested by respondents were: provider education (41%), regular updates of local sensitivity data (33%), patient education (26%), treatment guidelines/antibiotic protocols (22%) and restricting antibiotic use (regulation and treatment guidelines) (18%). Other strategies suggested included regular updates on prescription trends, faster laboratory turnaround time and treating only after culture is obtained.

Discussion

While the literature attributes high use of antibiotics to prescribers, information concerning antibiotic prescribing practices in Namibia is minimal, despite the 3rd National Medicines Use survey conducted among 1 132 patients in Namibia demonstrating that the use of antibiotics in the public health sector of Namibia increased from 39% in 1997 to 51% in 2001[15] and a study conducted in the private sector of Namibia in 2013 also showing that 80% of patients reported having used at least one antibiotic in the past year preceding the study (Pereko et al., unpublished). This study was the first to determine the choices clinicians make when faced with common infections in Namibia.

Our study achieved a response rate of 10%, which is comparable and in some instances higher than the response rate reported by others.[15–17] The following discussion therefore must be considered in the context of the low response rate.

The study uncovered that practices relating to antibiotic prescribing were the same across prescribers, largely in private practice, and were not influenced by age, years of practice, provider type, number of patients and region. The practice was also the same regardless of whether respondents had Namibian Standard Treatment Guidelines (STGs) or not. The literature is still divided on whether these factors influence prescribing or not. For example, in line with these findings, some authors found that sex and provider type had no influence on behaviour,[18] while others reported that younger doctors were more likely to prescribe antibiotics than older doctors.[19,20] Similarly, some authors reported that doctors with fewer years of experience were more likely to prescribe antibiotics than their counterparts with longer experience[20,21] while others reported the opposite.[22,23]

Our study found that workload had no effect on antibiotic prescribing practice. However, other studies reported that high patient volumes resulted in high antibiotic prescribing.[6,18,22,24] Similarly, looking at other studies we would have expected to find variations in prescribing practices based on qualifications and region of practice.[7,20–22,25,26]

For all listed infections, doctors treat empirically. This is consistent with literature findings which stated that fear was one of the factors influencing behaviour.[18,20,24,27] In these studies, doctors generally reported fear of the development of serious

complications if they waited before starting treatment. This is further supported by the fact that some of our respondents indicated the need for quicker laboratory turnaround time and stated this as a strategy that could reduce antibiotic use. The same sentiments were shared by other authors.[6,19]

While a variety of antibiotics are the reported first-line choice of prescribers, the most commonly used were the combination of amoxicillin with clavulanic acid, hereafter referred to as co-amoxiclav, amoxicillin and ciprofloxacin. The patterns of first choice of antibiotics observed in this study are similar to assessment of antibiotic consumption reported in other studies of different methodologies.[28,29]

For all infections, the reported preferred choices of antibiotics were not in line with the STGs. Most of the deviation was the use of second-line antibiotics instead of the first-line choice according to the STGs. Again, these findings are not peculiar to Namibia.[26,29] It is not clear what informs the doctors in their choice of antibiotic because, for almost all presented infections, their choice is in line with neither the recommendations as set out in the STGs nor the local/regional laboratory data. For example, *Escherichia coli* is the most frequent pathogen for UTI. The STG recommends the use of nitrofurantoin as first-line agent for the treatment of cystitis and the laboratory data show 95% sensitivity of *Escherichia coli* to this agent. Similarly, a study conducted in neighbouring South Africa also reported high sensitivity of *Escherichia coli* to nitrofurantoin (91.7%).[26] Local laboratory data show only 68% sensitivity of *E. coli* to the respondents' first choice, ciprofloxacin. Similarly, the STG recommends amoxicillin as first-line treatment for respiratory tract infections with the exception of pharyngitis. Laboratory data showed high sensitivity to amoxicillin and penicillin of most of these pathogens, thus confirming the STG recommendations.

When it comes to otitis media, the doctors' choice of co-amoxiclav is sensible. *Haemophilus* has shown 80% sensitivity to amoxicillin and 95% sensitivity to co-amoxiclav. Because the doctors treat empirically, the choice of an agent that would cover offending pathogens even though it is not in accordance with the STGs is understandable.

Apart from not being in line with the national guidelines, the reported preference of co-amoxiclav for respiratory tract infections and ciprofloxacin for uncomplicated urinary tract infections is concerning. It indicates unnecessary use of broad-spectrum antibiotics, which could lead to additional selection pressure favouring resistance.

This mismatch between respondents' first choice of agents and STGs and/or laboratory data is not surprising as the majority of respondents had indicated that they did not have STGs and that they also were not aware of the bi-annual sensitivity data made available by the private laboratory in Namibia. This lack of guidelines has been cited by others as a factor influencing practice.[16] The fact that the majority of doctors were not aware and did not have a copy of the STGs suggests that the distribution was not wide enough since these guidelines have been in effect since 2011, as was observed in the United Kingdom.[7] Furthermore, our study noted that there were no differences in choice of antibiotics between those who had STGs and those who did not. This shows that just having guidelines is not enough: there has to be a mechanism for ensuring use of these guidelines. This is supported by the respondents' suggestion to have 'guidelines that are enforced'.

As seen in this study, lack of access to local microbiology data can lead to doctors under-appreciating the prevalent levels of resistance and therefore using antibiotics with lower sensitivity. Second, doctors could overlook effective narrow-spectrum agents in favour of broad-spectrum antibiotics.

In an effort to understand what could be done to improve appropriate use of antibiotics, the study uncovered several factors "affecting prescribing of antibiotics". These factors included knowledge of local sensitivity patterns, restrictions on the availability and use of antibiotics and need for antibiotic guidelines/protocols.

The need for knowledge of local sensitivity patterns is not peculiar to our respondents. Doctors in the Democratic Republic of Congo and Peru expressed the same need and went further to suggest that this was essential for good prescribing.[9,30] A study in Brazil found that physicians generally underestimated the prevalence of resistance in their area.[29] Such underestimation could lead to patients being prescribed ineffective antibiotics. This was proved in this study by the respondents' preferred first choice for treating UTI, which was shown to be not as effective against *E. coli*. In Namibia, the sensitivity data are available. However, few doctors reported being aware of such data. Our recommendation is that sensitivity data be generated regularly and be disseminated through professional associations and also presented through continuing professional development (CPD) training.

The call for restrictions on the availability and use of antibiotics suggests that the choices for doctors are too wide and could therefore favour inappropriate use of antibiotics. It has been reported that increased availability resulted in newer and multiple antibiotics being prescribed.[18,34] In this study we observed that respondents unnecessarily prefer broad-spectrum to effective narrow-spectrum antibiotics, which could lead to antibiotic resistance selection pressure. Dumpis and colleagues also noticed similar preference in their study in Latvia.[31] Our recommendation therefore is for guidelines that would advocate for restriction in the use of antibiotics. The effectiveness of such a strategy, if implemented, has been reported by others. A study conducted in Peru indicated that the need to seek approval to use certain antibiotics was a deterrent that made prescribers seek other alternatives.[30] Similarly, doctors in Scotland and France reported finding the strategy of restricting prescriptions most helpful.[32] Guidelines would then have to be precise regarding the restrictions.

As with the need for local sensitivity patterns, the need for antibiotic guidelines has been expressed by many.[6,19,33,34] Others have also indicated that while there may be international guidelines, local guidelines are most preferable.[23,30] Others have gone as far as to suggest that an antibiotic formulary is among the main intervention methods for reducing the development and spread of resistance.[27] Namibia has both national STGs and antibiotic guidelines developed by the laboratory, which are accessible on the internet. However, the majority of the respondents did not have a copy of these guidelines. This emphasises that having guidelines is not enough; they would need to be well publicised and disseminated.

Our results have identified areas for future interventions to promote appropriate use of antibiotics in Namibia.

Conclusion

Our study uncovered that antibiotic prescribing practice was the same across various demographic groups. The advantage of this

is that the same interventions may be introduced without having to tailor for specific groups.

Second, the study uncovered prescribing practices that are not in line with current STGs and/or local sensitivity data. This may be due to the fact that most respondents did not have copies of guidelines and were not aware of the availability of local sensitivity data. This calls for rigorous dissemination of both guidelines and local sensitivity data. However, the study further found that even those doctors who had STGs did not prescribe in accordance with the guidelines, thus indicating the need for training on guidelines and strategies to ensure implementation of guidelines.

Acknowledgements – The authors wish to acknowledge the participants in the study and Dr Braam van Greunen.

Note

i. Member of the Global Respiratory Infection Partnership (GRIP) sponsored by Reckitt and Benckiser.

References

1. Alanis AJ. Resistance to antibiotics: are we in the post-antibiotic era? Arch Med Res. 2005;36:697–705. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16216651 http://dx.doi.org/10.1016/j.arcmed.2005.06.009
2. Mollahaliloglu S, Alkan A, Dornetas B, et al. Assessment of antibiotic prescribing at different hospitals and primary health care facilities. Saudi Pharm J. 2012;21:281–91.
3. World Health Organisation. Antimicrobial resistance: global report on surveillance. Geneva: World Health Organization; 2014.
4. Van Boeckel TP, Gandra S, Ashok A, et al. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. Lancet Infect Dis. 2014;14:742–50. http://dx.doi.org/10.1016/S1473-3099(14)70780-7
5. Lancet Infectious Disease Commission. Antibiotic resistance – the need for global solutions. Lancet Infect Dis. 2013;13:1057–98.
6. Adorka M, Dikokole M, Mitonga KH, et al. Healthcare providers attitudes and perceptions in infection diagnosis and antibiotic prescribing in public health institutions in Lesotho: a cross-sectional survey. Afr Health Sci. 2013;13(2):344–50.
7. Ali MH, Kalima P, Maxwell SRJ. Failure to implement hospital antimicrobial prescribing guidelines: a comparison of two UK academic centres. J Antimicrob Chemother. 2006;57:959–62. http://dx.doi.org/10.1093/jac/dkl076
8. Chandy, S.J. Consequences of irrational use of antibiotics. Indian J Med Ethics. 2008;V(4):174–275.
9. Hashemi S, Nasrollah A, Rajabi M. Irrational antibiotic prescribing – a local issue or a global concern? Exp Clin Sci Int J. 2013;12:384–95.
10. Dellit TH, Owens RC, McGowan Jr JE, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis. 2007;44:159–77. http://dx.doi.org/10.1086/510393
11. Pulcini C, Cua E, Lieutier F, et al. Antibiotic misuse: a prospective clinical audit in a French university hospital. Eur J Clin Microbiol Infect Dis. 2007;26:277–80. http://dx.doi.org/10.1007/s10096-007-0277-5
12. Lucet J, Nicolas-Chanoine M, Roy C, et al. Antibiotic use-knowledge and perceptions in two university hospitals. J Antimicrob Chemother. 2011;66:936–40. http://dx.doi.org/10.1093/jac/dkq541
13. O'Hanlon B, Feely F, De Beer I, et al. Namibia private sector assessment. Bethesda, MD: Strengthening Health Outcomes through Private Sector, Abt Associates Inc.; 2010.
14. Ministry of Health and Social Services. National Medicines Policy. 2nd ed. Namibia: Windhoek; 2011.
15. Lates J, Shiyandja N. 3rd National survey on the use of drugs in Namibia's public health institutions including monitoring the implementation of the National Drug Policy. Windhoek: Ministry of Health and Social Services. 2001.
16. Aitken C, Power R, Dwyer R. A very low response rate in an on-line survey of medical practitioners. Aust New Zealand J Public Health. 2008;32(3):288–9. http://dx.doi.org/10.1111/j.1753-6405.2008.00232.x
17. Crouch S, Robinson P, Pitts M. A comparison of general practitioner response rates to electronic and postal surveys in the setting of the National STI Prevention Program. Aust New Zealand J Public Health. 2011;35(2):187–9. http://dx.doi.org/10.1111/azph.2011.35.issue-2
18. Teixeira Rodrigues A, Roque F, Falcão A, et al. Understanding physician antibiotic prescribing behaviour: a systematic review of qualitative studies. Int J Antimicrob Agents. 2013;41:203–12. http://dx.doi.org/10.1016/j.ijantimicag.2012.09.003
19. Dooling K, Kandeel A, Hicks LA, et al. Understanding antibiotic use in Minya District, Egypt: physician and pharmacist prescribing and the factors influencing their practices. Antibiotics. 2014;3:233–43. http://dx.doi.org/10.3390/antibiotics3020233
20. Velasco E, Espelage W, Faber M, et al. A national cross-sectional study on socio-behavioural factors that influence physicians' decisions to begin antimicrobial therapy. Infection. 2011;39:289–97. http://dx.doi.org/10.1007/s15010-011-0137-1
21. Bharathiraja R, Sridharan S, Chelliah LK, et al. 2005. Factors affecting antibiotic prescribing pattern in pediatric practice. Indian J Paediatr. 2005;72(10):877–879 http://dx.doi.org/10.1007/BF02731121
22. Cadieux G, Tamblyn R, Dauphinee D, et al. Predictors of inappropriate antibiotic prescribing among primary care physicians. Can Med Assoc J. 2007;177(8):877–83. http://dx.doi.org/10.1503/cmaj.070151
23. Thriemer K, Katuala Y, Batoko B, et al. 2013. Antibiotic prescribing in DR Congo: a knowledge, attitude and practice survey among medical doctors and students. Plos One. 2013;8(2):e55495
24. Kotwani A, Holloway K. Trends in antibiotic use among outpatients in New Delhi, India. BMC Infect Dis. 2011;11(1):99–107. http://dx.doi.org/10.1186/1471-2334-11-99
25. Cutts C, Tett SE. Influencers on doctors' prescribing: is geographical remoteness a factor? Aust J Rural Health. 2003;11:124–30.
26. Lewis DA, Gumede LYE, Van der Hoven LA, et al. Antimicrobial susceptibility of organisms causing community-acquired urinary tract infections in Gauteng Province, South Africa. South Afr Med J. 2013;103(6):377–81. http://dx.doi.org/10.7196/samj.6722
27. Hulscher MEJL, van der Meer JWM, Grol RPTM. Antibiotic use: how to improve it? Int J Med Microbiol. 2010;300:351–6. http://dx.doi.org/10.1016/j.ijmm.2010.04.003
28. Achermann R, Suter K, Kronenberg A, et al. Antibiotic use in adult outpatients in Switzerland in relation to regions, seasonality and point of care tests. Clin Microbiol Infect. 2010;17(6):855–61. doi: 10.1111/1469.0691.2010.03348.x.
29. Murphy M, Bradley CP, Byrne S. Antibiotic prescribing in primary care, adherence to guidelines and unnecessary prescribing – an Irish perspective. BMC Fam Pract. 2012;13:43–50. http://dx.doi.org/10.1186/1471-2296-13-43
30. Garcia C, Llamocca LP, Garcia K, et al. Knowledge, attitudes and practice survey about antimicrobial resistance and prescribing among physicians in a hospital setting in Lima, Peru. BMC Clin Pharmacol. 2011;11:18. http://dx.doi.org/10.1186/1472-6904-11-18
31. Dumpis U, Dimiņa E, Akermanis M, et al. Assessment of antibiotic prescribing in Latvian general practitioners. BMC Fam Pract. 2013;14:9–13. http://dx.doi.org/10.1186/1471-2296-14-9
32. Pulcini C, Williams F, Molinari N, et al. Junior doctors' knowledge and perceptions of antibiotic resistance and prescribing: a survey in France and Scotland. Clin Microbiol Infect. 2011;17:80–7. http://dx.doi.org/10.1111/j.1469-0691.2010.03179.x
33. Guerra CM, Ramos MP, Penna VZ, et al. Perceptions and attitudes of the professional staff concerning infection surveillance and control programs in Brazilian hospitals. Am J Infect Cont. 2010;38:59–62. http://dx.doi.org/10.1016/j.ajic.2009.05.011
34. Jaruseviciene L, Radzeviciene Jurgute R, Bjerrum L, et al. Enabling factors for antibiotic prescribing for upper respiratory tract infections: perspectives of Lithuanian and Russian general practitioners. Upsala J Med Sci. 2013;118:98–104. http://dx.doi.org/10.3109/03009734.2013.778925

Received: 17-10-2014 Accepted: 25-02-2015

3.5. Chapter summary

In this chapter, the results of the study were presented in the form of four manuscripts. The first manuscripts presented how and which antibiotics are used in the private sector of Namibia. The second manuscript presented the sensitivity patterns of common pathogens and correlated the relationship between antibiotic use and the development of resistance. The third manuscript presented the findings of what the general public knows and how they use antibiotics. The final manuscript presented the practices of doctors as it relates to prescribing antibiotics for common community infections.

The next chapter will summarise the conclusions and recommendations of the study.

Chapter 4: Conclusion and Recommendations

4.1. Introduction

The overall aim of the study was to understand antibiotic usage and resistance patterns in the private health sector of Namibia. To this end, a two dimensional research approach was used, a literature review and an empirical study.

The results of the empirical study were presented in the previous chapter. This chapter will give a conclusive, integrative summary of the results in relation to the objectives the study sought to accomplish. The chapter also lists the limitations and makes recommendations as deduced from the study findings.

4.2. Conclusions and key findings deduced from the literature review

The following conclusions and key findings can be made from the literature objectives.

4.2.1. Scope magnitude and impact of antibiotic resistance

The first objective of the literature review was to investigate the scope, magnitude and impact of antibiotic resistance globally and in Namibia.

Antibiotics are among the most commonly used drugs for human use both in the developed and developing countries and their use continues to increase. Unfortunately, this increased use threatens many health gains including the decrease in morbidity and mortality due to infectious disease due to the development of resistance (Ashley *et al.*, 2011:1167; CDC, 2013:11).

Antibiotic resistance – the ability of microbes to grow in the presence of a medicine that would normally kill them or limit their growth – is a global health concern and has been identified as the greatest risk to human health (World Economic Forum, 2013:29 -32). Of greater concern is that the development of resistance outpaces the innovation and development of new drugs, which, if not corrected, could lead to a post-antibiotic era where common infections will no longer have a cure (WHO, 2011). Of great concern are

the “ESKAPE” pathogens, so named to identify them as well as to emphasise their ability to escape the lethal action of antibiotics (Rice, 2008: 1079). These pathogens are responsible for two thirds of all hospital infections in the US and their scourge is felt everywhere including developing countries (Lancet Infectious Diseases Commission, 2013:2; Nelson *et al.*, 2009:6; Vlieghe *et al.*, 2009:1).

Resistance is costly as it exerts economic strain on both the individual and the health system (Lancet Infectious Diseases Commission, 2013:3). Costs associated with resistance include morbidity and mortality, prolonged hospitalisation and complications; and the need for more expensive treatment options (CDC, 2013:11). In 2013, the Centre for Disease Control and Prevention (CDC) estimated the cost on the US economy due to antibiotic resistance to be in excess of $20 billion (CDC, 2013:11). The cost of treating drug-resistant TB in South Africa is estimated to be 103 times more than treating drug-sensitive TB (Pooran *et al.*, 2013: 8). Other costs associated with resistance are socio-economic costs such as loss of quality of life and loss of productivity due to illness. These costs are not easily recognised and therefore often forgotten when doing costing studies. The World Economic Forum Global Risk report reported the societal cost associated with antibiotic resistance in Thailand to be $2 billion per year (World Economic Forum, 2013:30).

Not many studies on antibiotic use and resistance have been conducted in Namibia. However, similar to global trends, the documented studies have shown that antibiotic use in the Namibia public sector increased by 12% between 1997 and 2001 (Lates & Shiyandja 2001:10). Resistance profiles were similar to those observed globally. For example, *E. coli* showed high rates of resistance to amoxicillin (79%), co-trimoxazole (78%) and nalidixic acid; while *N. gonorrhoeae* showed 24% resistance to ciprofloxacin (Lewis, 2011: 219).

The development of antibiotic resistance is a public health concern globally and in Namibia. Resistant organisms are found in hospital and community settings in both developed and developing countries. Resistance has clinical, economical and societal consequences.

4.2.2. Global strategies for addressing antimicrobial resistance

Given the threat posed by the development of antibiotic resistance, efforts to reduce antimicrobial resistance are a major point of focus by the World Health Organization and countries alike. In 2001, the WHO (WHO, 2012b: 8-10) launched the first antimicrobial resistance (AMR) strategy with interventions aimed at the patient, provider, health system and the environment (WHO, 2012b: 8-10). In 2014, the draft global action plan to combat AMR was drafted which details clear actions that should be taken to combat AMR. Both these documents highlight the following as important strategies in combating AMR (WHO, 2014:6):

- Improved awareness of AMR through education and training.
- Improved surveillance and research to better understand AMR locally and globally.
- Infection prevention and control measures to reduce the risk of AMR.
- Optimise use of antibiotics in both human medicines and animals through regular surveillance, promoting rational use and regulation.
- Develop business case for investment in new drugs and other interventions.

Coordinated efforts at country level and globally to implement these strategies to combat AMR are needed.

4.2.3. Namibia health system and the management of antibiotics

Namibia has a dual health system – public and private. The public health sector has adopted the principles of primary health care and services in approximately 85% of the population mainly those of lower income (WHO, 2010b). Health care in the public sector is accessed at a nominal fee (which varies depending on the level of care) and covers consultations, tests and medication. Quality of care in the public sector is good, however; the sector is overstretched and suffers from lack of health care workers especially doctors and pharmacists. The private health sector caters for the remaining 15% of the population. These mainly are employed persons and their beneficiaries. Health care in the private sector is covered through medical aid which is offered by

majority of employers (PharmAccess Foundation, 2011: 26). Seventy-two percent (72%) of doctors and 89% of pharmacists practice in the private sector (O'Hanlon *et. al*., 2010:28; WHO, 2011:120).

Management of medicines in Namibia is controlled by the Medicines and Related Substances Control Act (13 of 2003) and the National Medicines Policy (MoHSS, 2011a). The policy addresses factors that impact on delivery and use of pharmaceuticals in both the public and private sector such as legislation and regulation; drug procurement and distribution; the appropriate use of drugs by health workers and consumers; human resources development; and drug pricing and financing. Containing the emergence of AMR is a specific objective in the National Medicines Policy (NMP) (MoHSS, 2011a:5).

The regulation of the use of medicines is Namibia is done through the Namibia Medicines Regulatory Council (NMRC), a statutory body established in terms of the Medicines and Related Substance Control Act (13 of 2003). There are four sections under the NMRC, viz., inspection and licensing, medicines registration, quality surveillance laboratory and the therapeutic information and pharmacovigilance centre (TIPC). Medicines can only be imported and sold in Namibia if they are registered and can only be sold by registered persons (pharmacists) or authorised persons. Antibiotics are schedule 2 medicines and can only be sold upon prescription from an authorised prescriber (doctor who is registered in Namibia).

Compliance and enforcing of Act 13 of 2003 is done by the Inspection and licensing section of the NMRC through routine inspections of facilities, distribution and retail outlets and border posts. Quality of medicines coming into Namibia through the Central Medical Stores – the central procurement store for the public sector – is routinely monitored by the quality and surveillance laboratory (QSL). There are no quality checks conducted on medicines sold in the private sector. The TIPC is responsible for promoting the safe and appropriate use of medicines.

In the public sector, choice of medicines, including antibiotics is guided by the Namibia essential medicines list (Nemlist) and the National Standard Treatment Guidelines (STG). These documents, while meant for both the public and private sector, are not implemented in the private sector.

While strategies are in place to ensure regulation of medicines in Namibia, most of these are only applied in the public sector thus rendering the private sector less regulated. With less regulated and no surveillance in the private sector there are greater chances of inappropriate use of medicines including antibiotics.

4.3. Conclusions and key findings deduced from the empirical study

The following conclusions can be made from the objectives of the empirical studies as presented in the four articles.

4.3.1. Identifying and/or evaluating data sources for the quantification of antibiotic usage patterns in ambulatory patients in the private health sector of Namibia

The first objective of the empirical study was to optimise the research methodology for quantifying antibiotic usage patterns in ambulatory patients. The results of this study are presented in the article “Surveillance of Antibiotic Use in the private sector in Namibia using wholesale and claims data”

In understanding trends in antibiotic consumption, the study employed two data sources – medicines claims and wholesale. Both these methods have been used successfully independently and together for antibiotic consumption studies. The use of the two sources provided triangulation and thus increases the credibility and validity of the results. The WHO ATC/DDD methodology was used to quantify antibiotic use.

The study uncovered an increase in antibiotic use in the Namibia private health sector over the study period (2008 – 2011). The prescription claims data showed this increase to be 25% while the wholesale data showed this increase to be 57%. The increase in antibiotic use in keeping with global trends, Van Boeckel and colleagues (2014:744)

reported a global increase of antibiotic use of 36% (Van Boeckel *et al.*, 2014:744). The observed increase in antibiotic use in Namibia occurs while there is no corresponding increase in population (only 9% increasein population on medical aid between 2008 and 2011) or change in disease burden (there were no available data suggesting that there was any increase in number of diseases). This implies that the same population is having greater exposure to greater quantities of antibiotics thus making for greater selective pressure favouring the development of resistance.

Not only is antibiotic use in the Namibian private health sector on the increase, but this study found that it is high (26.8 DDD/1000/day) according to the European Surveillance of Antimicrobial Consumption (ESAC) project classification (ESAC, 2010: 10 -12).

In keeping with health seeking behaviour among the Namibian population, the study found that the biggest consumers of antibiotics were females (Namibia Global Health Initiative, 2011: 4). This finding is further supported by the fact that there are more female beneficiaries covered by medical aid fund (therefore by inference, accessing healthcare in the private sector) than males (medical aid data, unpublished).

Other concerns relating to antibiotic use in the Namibia private sector is the preference of the use of broad spectrum antibiotics. The study found that outpatient care is highly dependent largely on three classes of antibiotics – penicillins (42%), cephalosporins (20%) and macrolides (19%) – and mainly on the broad spectrum agents in these classes. Again, this is in line with global trends; similar findings are reported in India, Israel, Italy, Malta, USA and the ESAC (Ferech *et al.*, 2006: 405; Kotwani *et al.*, 2011: 6; Lee *et al.* 2014: 7 – 8; Low *et al.,* 2013: 405; Vaccheri *et al.*, 2008: 956; Verspoetten *et al.*, 2014: 6).

Of the two methods used to determine antibiotic use in the private sector, the wholesale data were found to over-estimate antibiotic consumption. Similar findings were reported by other studies that used similar research method (Campos *et al* 2007: 701; Gagliotti *et al.*, 2009:1117; Kotwani *et al.*, 2009:558). The medicine claims data is the preferred method as it closely resembles prescriptions dispensed (prescription data) and is

therefore a more accurate estimation of usage between the two sources of data. Furthermore, the medicine claims data contains more information, such as patient and provider demographics that allow for more analysis than does the wholesale data. Both sets of data are not easy to collect and depend on the goodwill of the medical aid fund and the wholesalers and so require good coordination preferably from the government.

The method employed is good for estimating antibiotic usage in the Namibian private sector. However, in a country with a dual healthcare system, it gives only part of the picture. To get the full picture of antibiotic use in Namibia, the methodology should be expanded to include data from the public sector perhaps using the INRUD/WHO methodology on investigating drug use in health facilities.

This objective has been met.

4.3.2. Ascertaining susceptibility patterns in the private health sector and determine possible relationships between antibiotic usage and resistance

The results of the second objective “ascertaining susceptibility patterns in the private health sector and determining possible relationship between antibiotic resistance and usage” were presented in Manuscript 2: Antibiotic use and resistance in the Namibia private health sector.

Quantification of antibiotic use in the private sector of Namibia uncovered very high use of antibiotics (27 DDD/1000/day). Given the documented association between high use of antibiotics and the development of resistance in literature (CDC, 2013:11; Gallini *et al.*, 2010: 265; Kotwani *et al.*, 2009: 555; Vernaz *et al.*, 2011: 933), such high use of antibiotics observed in Namibia is logically expected to result in development of resistant pathogens.

Building on the antibiotic use review conducted, laboratory antibiotic sensitivity data were collected and analysed to determine whether there was any association between antibiotic use and sensitivity. Data provided were from 2001 to 2011 with a gap in data between 2005 and 2010.

The study found overall modest changes in sensitivities over the years. However, increasing resistance in older antibiotic agents was observed compared to newer agents – findings similar to those reported in 2005 in South Africa (Essack *et al.*, 2005:867).

Overall resistance was observed to amoxicillin (40%), chloramphenicol (82%) and co-trimoxazole (47%); and reduced sensitivity observed for amoxicillin with clavulanic acid, (22%) nalidixic acid (27%), erythromycin (26%) and tetracycline (26%). Sensitivity profiles observed in the study are similar to those reported elsewhere in Africa (Alabi *et al.*, 2013:4; Ameko *et al.*, 2012:68; Ashley *et al.*, 2011: 1168 - 1170; Mengistu, 2014: 11; Tirunneh *et al.*, 2013:4).

The study found that there was no significant correlation between antibiotic use and resistance for data collected in the same year (p = 0.867). However, correlating earlier antibiotic use with resistance prevalence for later years showed correlation trends approaching significance (decrease in p-value from p = 0.856 in 2010 to p = 0.056 in 2011) implying that prior antibiotic use has an impact on current and future resistance (Gallini *et al.*, 2010: 2655; Krotsotakis *et al.*, 2008: 752; Mohamat *et al.*, 2005: 303-306).

The study further found that as the volume of antibiotics increases, the time required to reach resistance reduced (p=0058). This confirms findings reported in literature that volume of antibiotics increases the selection pressure for the development of resistance (Bell *et al.*, 2014:25; Costelloe *et al.*, 2010:11; Goossens 2005:583).

Antibiotic use does have an impact on the development of resistance. At community level while antibiotic use may not have an immediate impact on the development of resistance, it does have an impact on future resistance. Increased use of antibiotics in Namibia will compromise choice of antibiotics available for treatment of infections.

This objective has been met.

4.3.3. Determining the perceptions of private doctors (general practitioners and specialists) their behaviour and clinical practice in prescribing antibiotics

The use of antibiotics, among others is influenced by prescribers. The third objective therefore was to determine the perceptions of private doctors, their behaviour and clinical practice in prescribing antibiotics. The results of this study were presented in the published article “Antibiotic use in Namibia: prescriber practices for common infections”.

The component of this study that determined antibiotic consumption revealed high antibiotic use in the private sector. High use of antibiotics has been largely attributed to prescribing practices especially inappropriate prescribing of antibiotics (Adorka *et al.*, 2013:344; Hasheni *et al.*, 2013: 385; Kheder 2013:348). In this phase of the study, a cross-sectional survey using self-administered questionnaires was conducted to determine the behavior and practices of prescribers in relation to antibiotics prescribing.

The findings of the study revealed that possession of national standard treatment guidelines (STG) and the awareness of local sensitivity data were poor among the private doctors (31% and 20% respectively). This was evidenced by their choices of antibiotics for common community infections, which were neither in line with STG nor local sensitivity data. Both the lack of guidelines and sensitivity data have been cited as a factor influencing practice (Dooling *et al.*, 2014:239; Guerra *et al.* 2010:5; Thriemer *et al.*, 2013:5).

The general practice among the prescribers (77%) was to treat common community infections empirically, a finding consistent with literature (Hulscher *et al.*, 2010:353; Kotwani *et al.* 2010:686; Rodriguez *et al.*, 2013: 208; Velasco *et al.*, 2011:294). This was said to be influenced by the long laboratory turn-around time.

The prescribers preferred broad spectrum antibiotics for treatment of common infections and the most common antibiotic of choice were amoxicillin with clavulanic acid, amoxicillin and ciprofloxacin. These choices validate what was uncovered in the first

phase of this study that explored trends in antibiotic usage and are in line with what other authors found (Hasheni *et al.* 2013:388; Murphy *et al.;* 2012:3).

The lack of STG and knowledge of local sensitivity data has an impact on the prescribing patterns of doctors as their choice of antibiotics were not in line with either the STG or sensitivity data.

This objective has been met.

4.3.4. Examining the perceptions of the public their behaviour regarding antibiotics use in the community of Windhoek

In this phase of the study set out to determine what the community understands about antibiotics and how they tend to use them. With this in mind, this section of the study therefore examined Windhoek community's understanding and behaviour in relation to antibiotics and their use. The results of this study are presented in the article "Public knowledge, attitudes and behaviour towards antibiotic usage in Windhoek, Namibia".

Overall, the study uncovered that there was high use of antibiotics in the private sector in Windhoek (80%) particularly for respiratory tract infections. This finding is consistent with the results of the first phase of the study that quantifies trends in antibiotic usage which found high antibiotic use nationally and in Windhoek. Respiratory tract infections have been cited as the most commonly treated acute problem in primary care (Velden *et al.*, 2013: 323) thus further validating the findings of this study.

Patients' behaviour towards antibiotics was generally positive with the majority (85%) of them receiving antibiotics only by doctors' prescription and the majority (81%) completing their antibiotic course. In this regard, the respondents in this study performed better than respondents in other similar studies in Malaysia, Taiwan, Nigeria, Omen, Jordan, Hong Kong and South Korea) (Auta *et al.*, 2013: 1090; Jose *et al.*, 2013:326; Oh *et al.*, 2011: 344; Suiafan *et al.*, 2012:767; Sun *et al.*, 2011: 744; Yah *et al.*, 2008: 82; You *et al.*, 2008: 156).

Patients do not generally request antibiotics when visiting a doctor (85%). However, self-medication (15%) with antibiotics, especially among patients with medical aid, was observed. Self-medication with antibiotics has been reported to be a common phenomenon in both developed and developing countries (Llor & Cots, 2009:1345; Morgan *et al.,* 2011: 693). Majority (82%) of the self-medicating patients bought their antibiotics from the pharmacy without a prescription, again a finding not unique to Namibia and well documented in literature (Auta *et al.*, 2013:1089; Belkina *et al.*, 2014:425; Jose *et al.* 2013:324; Shehadeh *et al.,* 2011:131).

Gaps in the general population knowledge of antibiotics and their use were also observed. This was most pronounced as a good proportion (64%) believing that antibiotics are effective against viruses and this is evidenced by their expectation of antibiotics to cure cold. Once again, these findings mirror those reported in literature (Andre *et al.*, 2010: 1295; McNulty *et al.*, 2007a: i64; McNulty *et al.*, 2007b: 736; Oh *et al.*, 2011: 343-345; Sun *et al.*, 2011: 744).

There is a high use of antibiotics in Windhoek particularly for respiratory tract infections. Patients' behaviour towards antibiotics is generally positive with the majority of them receiving antibiotics only by doctors' prescription and the majority completing their antibiotic course. The public showed poor knowledge of antibiotics especially with regards to their use for viral infections. The public showed a good knowledge of the relationship between antibiotic resistance and unnecessary use of antibiotics. Educating the public on antibiotics and their proper use is essential in improving prudent their prudent use.

This objective has been met.

4.4. Limitations

The study had several important limitations:

- Data collected on antibiotic use did not contain diagnosis/clinical data therefore it was impossible to determine if the high use of antibiotics observed was appropriate or not for the specific diagnosis.
- Antibiotic use data presented represents only about 9% of the total Namibian population (54% of the private health care population) and does therefore not provide a full picture of the antibiotic consumption in Namibia. The conclusions can therefore only be made for the study populations (i.e. not generalizable to the whole population of Namibia).
- Not all wholesale data were available for analysis of antibiotic usage. While this did not affect the trends observed, it affected the usage quantities observed.
- Laboratory sensitivity data for 2008 and 2009 was missing and therefore affected year on year comparisons between usage and sensitivity.
- Laboratory data could not be disaggregated between outpatient and inpatient. Therefore private sector outpatient antibiotic usage data were compared with aggregated sensitivity data.
- Both the doctor and public surveys were self-reporting and as with all self-reporting studies, participants may have given socially desirable responses.
- The small number of participants in the doctor survey limits the generalizability of the results (Kellerman & Herold, 2001: 61; Nichols *et al.*, 2011: 1676; Pit *et al.*, 2014:1; VanGeest *et al.*, 2007: 304).
- The public survey assumed that the respondents were familiar with the term “antibiotic” and in the knowledge section, did not ask any questions to verify such knowledge.
- The public survey used few questions to assess knowledge and attitudes (beliefs) of the general population.

4.5. Strengths

The main strength of the study lies in the fact that it underscored the fact that antibiotic use and resistance are influenced by many factors. The study therefore employed multiple research methodologies to understand antibiotic usage in the context of Namibia from multiple facets. From the literature review, the study sought to understand the Namibia health system. This helped understand the burden of diseases and the legal framework that influences antibiotic usage and could therefore impact on the development of resistance.

This is the first study that attempted to uncover antibiotic use, resistance, practices and knowledge of prescribers and the public in Namibia. The findings of this study therefore form a baseline for any other antibiotic studies that will be carried out in the future in the private sector of Namibia.

4.6. Recommendations

The study unearthed several shortcomings and areas of concern in relation to antibiotic usage in the private sector of Namibia. Based on those findings, the following recommendations are made:

- Surveillance:
  In line with the WHA Global Action Plan, regularly monitor resistance trends of set of core organisms and report nationally and globally. This should be combined with regular antibiotic consumption.
  The surveillance should be inclusive of both antibiotic use in the public and private sector. To allow for comparisons with other countries, the ATC/DDD methodology as employed in this study should be used to quantify antibiotic use. The results of the surveillance should be published and disseminated to all health care professionals. The results should also be submitted to WHO periodically.
- Regular dissemination of resistance data.
  The local laboratory generates and publishes sensitivity patterns bi-annually on the website. However, most respondents were not aware of this. It is recommended

therefore that this data be shared with all healthcare professionals through their respective associations. The caveat with this data is that it is only for private sector. In light of this, we recommend that all laboratories, both in the public and private sector, jointly put together sensitivity data and share this bi-annually with the health care professionals.

- Updating and dissemination of treatment guidelines.

  Namibia has treatment guidelines but the study showed poor possession (20%) of these by prescribers. The first step therefore should be a wide distribution of guidelines through professional associations or through medical representatives of pharmaceutical companies.

  Treatment guidelines should be updated regularly in line with the surveillance results so that they correspond to local trends of both antibiotic use and resistance.

- Devising strategies to ensure the implementation of guidelines.

  Pharmacies and medical aid funds (third party payers) are the two most likely mechanisms for enforcing adherence to guidelines. This would be a challenge in a dichotomous public and private healthcare setting like Namibia where prescribing is regulated in the public sector while there is no regulation of prescribing in the private sector. To address this dichotomy, a two-prong approach can be used. In public facilities, pharmacy personnel could be trained to monitor and ensure appropriate use of antibiotics in accordance with guidelines. In private practice, reimbursement by medical aid could be tied to compliance to guidelines. Additionally, like in the public sector, community pharmacists could dispense only if the prescription is in accordance with treatment guidelines unless the doctor provides a justification. Both these strategies would require that prescriptions indicate the diagnosis, a practice not implemented in Namibia even though it is mandate by law (Medicines and Related Substances Act, 13 of 2003).

- Regular continuing professional development (CPD) sessions on antibiotic usage trends, sensitivity and guidelines.

  Educating health professionals on antibiotic use and antimicrobial resistance is something that has been stressed in literature and also expressed by the

respondents. It is therefore recommended that local antibiotic usage trends are monitored regularly; that international antibiotic resistance bodies are used to source up to date information. These, together with sensitivity patterns should be part of regular continuing education. This could be undertaken by Namibians Against Antimicrobial Resistance (NAAR). CPD sessions do not have to be face- to-face. The Pharmaceutical Society of Namibia (PSN) had great success with training the pharmacists on national TB guidelines by using online case studies. This method should be considered when designing CPD trainings for professionals.

- Public education programs targeting areas of misconceptions and weaknesses.
  This intervention should focus on educating the public on illnesses that require antibiotic therapy, when antibiotics should be used and the importance of compliance.
- Tighter enforcement of the regulations.
  The study uncovered that there was over the counter sale of antibiotics which by law (Medicines and Related Substances Act, 13 of 2003) are meant to be prescription only medicines. Stricter reimbursement practices should be employed by the medical aid that would discourage patients purchasing antibiotics without a prescription. Regular inspections for sale of antibiotics without a prescription should be conducted and punitive measures for offenders effected.

A more in-depth study on factors influencing antibiotic prescribing should be conducted. The study should aim for more prescriber participants than what was achieved in this study. Sharing the findings of this study with all professionals could incentivise them to want to participate in future studies. The research methodology for such a study should be focus group discussions which will allows for in-depth probing and is likely to shed a better light on what influences prescribing of antibiotics. The study should also look at barriers to adherence to guidelines. This will help identify what interventions to promote prudent prescribing to put in place and how.

Additionally, since the public survey was conducted only in Windhoek, a more in-depth nationwide study should be conducted through Ministry of Health and Social Services.

4.7. Chapter Summary

This was the first study to assess antibiotic use in the private sector of Namibia. Moreover, it was the first study that aimed to understand trends in antibiotic usage and link this with factors affecting use as well as the development of resistance.

Antibiotic use is influenced by the health system, the legal environment, the health providers and the users. In turn, antibiotic use impacts the development of resistance. In this study, all these factors were studied.

The study uncovered high antibiotic use in the private sector with a preference for broad spectrum antibiotics. Prescriber and dispenser practices in the private sector show a crack in the enforcement of regulations and systems in a dichotomous health system, which lends itself towards inappropriate antibiotic use. Gaps in public knowledge about antibiotics were also observed. All these are ingredients for the development of resistance.

The study further showed that if antibiotic use trends continue in this fashion, the development of resistance is inevitable.

While Namibia has a well-developed health system and mechanisms in place for regulating the sale and use of antibiotics, the dual health system with a less regulated private sector leaves room for less than prudent use of antibiotics. Systems that restrict use of antibiotics in the public sector that are not implemented in the private sector could potentially allow for inappropriate use of antibiotics in this sector.

The findings of this study have important policy and public health implications for Namibia.

References list

Abasaeed, A., Vlcek, J., Abuelkhair, M. & Kubena, A. 2009. Self-medication with antibiotics by the community of Abu Dhabi Emirate, United Arab Emirates. *Journal of infection in developing countries,* 3(7): 491-497.

Academy of Managed Care Pharmacy (AMCP). 2009. Drug utilisation review. Alexandria, VA: Author.

Achermann, R., Suter, K., Kronenberg, A., Gyger, P., Muhlemann, K., Zimmerli, W. & Bucher, H.C. 2010. Antibiotic use in adult outpatients in Switzerland in relation to regions, seasonality and point of care tests. *Clinical microbiology and infection*, 17(6):855-861.

Acts ***see*** Namibia.

Adorka, M., Dikokole, M., Mitonga, K.H. & Allen, K. 2013. Healthcare providers' attitudes and perceptions in infection diagnosis and antibiotic prescribing in public health institutions in Lesotho: a cross-sectional survey. *African health sciences,* 13(2):344-350.

Adriaenssens, N., Coenen, S., Tonkin-Crine, S., Verheij, T.J.M., Little, P. & Goossens, H. 2011. European Surveillance of Antimicrobial Consumption (ESAC): disease-specific quality indicators for outpatient antibiotic prescribing. *BMJ quality and safety,* 20:764-772.

Afolabi, M. O., Macarthy, L. & Osemene, K.P. 2014. Use of antimicrobial medicines among university students in Sierra Leone. *British journal of pharmaceutical research,* 4(1):101-112.

Afzal Khan, A.K., Banu, G. & Reshma, K.K. 2013. Antibiotic resistance and usage – a survey of knowledge, attitudes, perceptions and practice among the medical students of a southern Indian teaching hospital. *Journal of clinical and diagnostic research,* 7(8):713-718.

Agarwal. N.K. 2011. Verifying survey items for construct validity: a two-stage sorting procedure for questionnaire design in information behaviour research. *ASSIST*: 1-8.

Ahmed, O.I., El-hady, S.A., Ahmed, T.M. & Ahmed, I.Z. 2013. Detection of bla SHV and bla CTX-M genes in ESBL producing Klebsiella pneumonia isolated from Egyptian patients with suspected nosocomial infections. *The Egyptian journal of medical human genetics*, 14:277-283.

Aiken, A. M., Mutuku, I. M., Sabat, A.J. Akkerboom, V., Mwangi, J., Scott, J.A. Morpeth, C.S., Friedrich, A. & Grundmann, H. 2014. Carriage of Staphylococcus aureus in Thika level 5hospital, Kenya: a cross-sectional study. *Antimicrobial resistance and infection control*, 3(22):1-7.

Aitken, C., Power, R. & Dwyer, R. 2008. A very low response rate in an online survey of medical practitioners. *Australian and New Zealand journal of public health*, 32(3):288-289.

Al-Dossari, K. 2013. Parental attitudes, knowledge and practice on antibiotic use for upper respiratory tract infections in children. *Majmaah journal of health sciences,* 1(1):39-51.

Alanis, A.J. 2005. Resistance to antibiotics: are we in the post antibiotic era*? Archives of medical research,* 36:697–705. http://www.ncbi.nlm.nih.gov/pubmed/16216651 Date of access: 5 April 2011.

Austin, D.J., Kristinsson, K.G. & Anderson, R.M. 1999. The relationship between the volume of antimicrobial consumption in human communities and the frequency of resistance. Abstract. *Proceedings of National Academy of Sciences of the United States of America,* 96(3):1152-1156.

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.

Alliance for the Prudent Use of Antibiotics (APUA). http://www.tufts.edu/med/apua/about_issue/ecology.shtml Date of access: 9 October 2012.

Alzoubi, K., Al-Azzam, S., Alhousban, A., Mukattash, T., Al-Zubaidy, S., Alomari, N. & Khader, Y. 2013. An audit on the knowledge, beliefs and about the uses and side-effects of antibiotics among outpatients attending 2 teaching hospitals in Jordan. *Eastern Mediterranean health journal,* 19 (5):478-484.

Ameko, E., Achio, S. & Alhassan, S. 2012. Effects of self-medication on the efficacy of four antibiotics commonly used in Ghana on clinically isolated micro-organisms. *International journal of pure and applied sciences and technology*, 10(2):62-70.

Anderson, D.R., Sweeney, D.J. & Williams, T.A., (Eds.). 2009. *Statistics for business and economics revised*. (10th ed.). Mason, OH: Thomson South-Western: 1081.

Andre, M., Vernby, A., Berg, J. & Lundborg, C. 2010. A survey on public knowledge and awareness related to antibiotic use and resistance in Sweden. *Journal of antimicrobial chemotherapy*, 1292-1296.

Anon. 2010. South-East Asia regional strategy for prevention and containment of antimicrobial resistance.

http://www.searo.who.int/LinkFiles/BCT_Regional_Strategy_ARM_ver31032010.pdf
Date of access: 7 October 2012.

Ansari, F., Erntell, M., Goossens, H. & Davey, P. 2006. The European surveillance of antimicrobial consumption (ESAC) point-prevalence survey of antibacterial use in 20 European hospitals in 2006. *Clinical infectious disease,* 49:1496-1504.

Apalata, T., Zimba, T. F., Sturm, W.A. & Moodley, P. 2009. Antimicrobial susceptibility profile of Neisseria gonorrhoeae isolated from patients attending a STD facility in Maputo, Mozambique. *Sexually transmitted disease*, 36 (6):341-343.

Ashley E.A., Lubell, Y., White, N.J & Turner, P. 2011. Antimicrobial susceptibility of bacterial isolates from community acquired infections in Sub-Sahara and Asian low and middle income countries. *Tropical medicine and international health*, 16(9):1167-1179.

Association for Professionals in Infection Control and Epidemiology (APIC). www.apic.org/Professional-Practice/Practice-Resources?Antimicrobial-Stewardship
Date of access: 25 March 2013.

Auta, A., Banwat S.B., David, S., Dangiwa, D., Ogbole, E. & Tor-ayiin, A. 2013. Antibiotic use in some Nigerian communities: knowledge and attitudes of consumers. *Tropical journal of pharmaceutical research,* 12(6):1087-1092.

Aziz, A. 2013. The role of healthcare strategies in controlling antibiotic resistance. *British journal of nursing,* 22(18):1066-1074.

Bala, R., Singh, H., Kaur, K., Girish, P. & Kohli, K. 2013. Knowledge and attitudes towards antibiotic self-medication usage: a cross sectional study among nursing and medical students. *International journal of basic and clinical pharmacology*, 2(4):428-432.

Bartlett, J. 2011. A call to arms: the imperative for antimicrobial stewardship. *Clinical infectious disease*, 53(S1):S4-S7.

Belkina, T., Al-Warafi, A., Eltom, E. H., Tadjieva, N, Kubena, A. & Vlcek, J. 2014. Antibiotic use and knowledge in the community of Yemen, Saudi Arabia and Uzbekistan. *Journal of infection in developing countries,* 8(4):424-429.

Bell B.G., Schellevis, F., Stobberingh, E., Goossens, H. & Pringle, M. 2014. A systemic review and meta-analysis on the effects of antibiotic consumption on antibiotic resistance. *Biomed central infectious diseases,* 14:13.

Belongia, E. A. Naimi, T.M., Gale, C.S. & Besser, R.E. 2002. Antibiotic use and upper respiratory infections: a survey of knowledge, attitude and experience in Wisconsin and Minnesota. *Preventive medicine,* 34:346-352.

Beovic, B. 2006. The issue of antimicrobial resistance in human medicine. *International journal of food microbiology*, 112:280-287

Bercion, R., Mossoro-Knipinde, D., Manirakiza, A. & Le Faou, A. 2009. Increasing prevalence of antimicrobial resistance among Enterobacteriaceae uropathogens in Bangui, Central African Republic. *Journal of infections in developing countries*, 3(93):187-190.

Bergman, M., Huikko, S., Huwinen, P. Paakkari, P. & Seppala, H. 2006. Macrolides and azithromycin use are linked to increased macrolide resistance in *Streptococcus pneumoniae*. *Antimicrobial agents and chemotherapy,* 50(11):3646-3650.

Bharathiraja, R., Sridharan, S., Chelliah, L.K., Suresh, S., Senguttuvan, M. 2005. Factors affecting antibiotic prescribing pattern in paediatric practice. *Indian journal of paediatrics*, 72(10):877-879.

Bosu, W.K. and Mabey, D. 1998. The availability and cost of antibiotics for treating PID in the Central Region of Ghana and implications for compliance with national treatment guidelines. *International journal of STD and AIDS. (*Abstract). http://ijsa.rsmjournals.com/cgi/content/abstract/9/9/551 Date of access: 21 August 2011.

Botma, Y., Greeff, M, Mulaudzi, M & Wright, S. 2010. Research in health sciences. Cape Town, Heinemann.

Boucher, H. W., Talbot, G.H., Bradley, J. S., Edwards, J.E., Gilbert, D., Rice, L.B., Scheld, M. Spellberg, B. & Bartlett, J. 2009. Bad bugs, no drugs: No ESKAPE! An update from the Infectious Disease Society of America. *Clinical infectious diseases,* 48:1-12.

Bremon, A.R., Ruiz-Tovar, M., Gorricho, B., De Torres, P. & Rodriquez, R. 2000. Non-hospital consumption of antibiotics in Spain: 1987–1997. *Journal of antimicrobial chemotherapy,* 45:395-400.

Brockmeyer, B. 2012. Health systems in Namibia – deliberations about affordable national health insurance for low-income workforce in Namibia. Windhoek, Namibia.

Bronzwaer, S.L., Cars, O., Buchholz, U., Molstad, S., Goettsch, W., Veldhuijzen, I.K., Kool, J.L., Sprenger, M.J.and Degener, J.E. 2002. A European study on the relationship between antimicrobial use and antimicrobial resistance. *Emerging infectious disease,* 8:278-282. http://www.cdc.gov/ncidod/eid/vol8no3/01-0192.htm Date of access: 5 April 2011.

Brown, L. B., Krysiak, R., Kamanga, G., Mapanje, C., Kanyamula, H., Banda, B., Mhango, c., Hoffman, M., Kamwendo, D., Hobbs, M., Hosseinipour, M.C., Martison, F., Cohen, M. & Hoffman, I. 2010. Neisseria gonorrhoeae antimicrobial susceptibility in Lilongwe, Malawi, 2007. *Sexually transmitted diseases*, 37(3):169-172.

Buke, A.C., Ermetcan, S., Hosgor-Limoncu, M., Ciceklioglu, M. & Eren, S. 2003. Rational antibiotic use and academic staff. *International journal of antimicrobial agents*, 21:63-68. http://www.ijaaonline.com/article/S0924-8579%2802%2900272-8/abstract Date of access: 10 May 2014.

Buke, C., Hosgor-Limoncu, M., Ermertcan, S., Ciceklioglu, S., Tuncel, M., Köse, T. & Eren., S. (2005). Irrational use of antibiotics among university students. *Journal of infection*, 51:135-139.

Burton, B. & Jesilow, P. 2011. How healthcare studies use claims data. *The open health services and policy journal,* 4:26-29.

Bustamante, N.D. 2011. MRSA – a global threat. Dallas UT Southwestern Medical School (Thesis – MD in international health).

Byarugaba, D. K. 2004. A view of antimicrobial resistance in developing countries and responsible risk factors. *International journal of antimicrobial agents*, 24:105-110.

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.

Campos, J., Ferech, M., Lazaro, E., De Abajo, F., Oteo, J., Stephens, P. & Goossens, H. 2007. Surveillance of outpatient antibiotic consumption in Spain according to sales data and reimbursement data. *Journal of antimicrobial chemotherapy,* 60:697-701.

Cao, V., Ratsima, E., Van Tri, D., Bercion, R., Fonkoua, M., Ricahrd, V. & Talarmin, A. 2008. Antimicrobial susceptibility of Neisseria gonorrhoeae strains isolated in 2004-2006 in Bangui, Central African Republic; Yaounde, Cameroon; Antananarivo, Madagascar; and Ho Chi Minh Ville and Nha Trang, Vietnam. *Sexually transmitted diseases*, 35 (11):941-945.

Carrie, A.G. & Zhanel, G.G. 1999. Antibacterial use in community practice: assessing quality, indications and appropriateness and relationship to the development of antibacterial resistance. *Drugs,* 57 (6):871-881. (Abstract). http://www.ncbi.nlm.nihn.gov/pubmed/10400402 Date of access: 3 January 2012.

Cars, O. & Nordberg, P. 2005. Antibiotic resistance – the faceless threat. *International journal of risk and safety in medicines*, 17:103-110.

Cars, O., Hedin, A. & Heddini, A. 2011. The global need for effective antibiotics – moving towards concerted action. *Drug resistance update,* 14:68-69.

Cartlett, J., Callignon, P., Goossens, H., Gyssens, I., Harbarth, S., Jallier, V., Levy, S.B., N'Doye, B., Pittet, D., Ritchmann, R., Seto, W.H., Van der Meer, J.W.M. & Voss, A. 2011. Society's failure to protect antibiotics. *Lancet,* 378:369–371.

Centres for Disease Control and Prevention (CDC), US Department of Health and Human Services. 2003. Questionnaire design. Georgia, AT, USA: Author.

Centres for Disease Control and Prevention (CDC), US Department of Health and Human Services. 2004? Antibiogram surveillance method using cumulative susceptibility data. Georgia, USA: Author.

Centres for Disease Control and Prevention (CDC), US Department of Health and Human Services. 2010. Antibiotic resistance and the threat to public health. Georgia, USA: Author.

Centres for Disease Control and Prevention (CDC), US Department of Health and Human Services. 2013. Antibiotic resistance threats in the United States. Georgia, USA: Author.

Chalker, J., Joshi, M., & Aboagye-Nyame, F. 2005. *Trip Report: Okahandja, Namibia PRDU Course, April 2005*. (Submitted to the US Agency for International Development

by the Rational Pharmaceutical Management Plus Program. Arlington, VA: Management Sciences for Health.)

Chambers H.F. 2006. General principles of antimicrobial therapy. (*In* Goodman and Gilman's *The pharmacological basis of therapeutics*). (11th ed). McGraw-Hill, New York.

Chandy, S.J. 2008. Consequences of irrational use of antibiotics. *Indian journal of medical ethics*, (4):174-175.

Chandy, S.J., Thomas, K., Mathai, E., Antonisamy, B., Holloway, K.B. & Landborg, C.S. 2013. Patterns of antibiotic use in community and challenges of antibiotic surveillance in a lower-middle-income country setting: a repeat cross sectional study in Vellore, south India. *Journal of antimicrobial chemotherapy,* 68:229-236.

Chen, D.K., McGeer, A., De Azavedo, J.C. & Low, D.E. 1999. Decreased susceptibility of Streptococcus pneumoniae to fluoroquinolones in Canada. Canadian bacterial surveillance network. *New England journal of medicine,* 341: 233-239. http://www.nejm.org/doi/full/10.1056/NEJM199907223410403 Date of access: 25 March 2011.

Chen, C., Chen, Y., Hwang, K., Lin, S., Yang, C., Tsay, R., Lui, C. & Young, T. 2005. Behaviour, attitudes and knowledge about antibiotic usage among residents of Changhua, Taiwan. *Journal of microbiology, immunology and infection,* 38: 53-59.

Clavenna A. & Bonati, M. 2011. Differences in antibiotic prescribing in paediatric outpatients. *Archives of diseases in childhood*. doi.10.1136/acd.2010.18354

Coenen, S., Ferech, M., Malhotra-Kumar, S., Hendrickx, E., Suetens, C. & Goossens, H. 2006a. European surveillance of antimicrobialconsumption (ESAC): outpatient macrolide, lincosamide andstreptogramin (MLS) use in Europe. *Journal of antimicrobial*

chemotherapy, 58:418-422.http://jac.oxfordjournals.org/content/58/2/418.full. Date of access: 6 April 2011.

Coenen, S., Ferech, M., Dvorakova, K., Hendrickx, E., Suetens, C. & Goossens, H. 2006b. European surveillance of antimicrobial consumption (ESAC): outpatient cephalosporin use in Europe. *Journal of antimicrobial chemotherapy,* 58:413-417. http://jac.oxfordjournals.org/content/58/2/418.full Date of access: 6 April 2011.

Coenen, S., Gielen., B., Blommaert, A., Beutels, P., Hens, N. & Goossens, H. 2013. Appropriate international measures for outpatient antibiotic prescribing and consumptions: recommendations from a national data comparison of different measures. *Journal of antimicrobial chemotherapy*, 2013, doi.101093/jac/dkt385.

Cohen, M. L. 1992. Epidemiology of drug resistance: Implications for a post-antimicrobiale era. *Science,* 257 (5073): 1050-1055. http://www.sciencemag.org/content/257/5073/1050.short. Date of access: 14 February 2012.

Costelloe, C., Metcalfe, C., Lovering., A., Mant, D. & Hay, A.D. 2010. Effect of Antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systemic review and meta-analysis. *British medical journal,* 340:c2096.

Costelloe, C., Williams, O.M., Montgomery, A.A., Dayan, C. & Hay, A. 2014 . Antibiotic prescribing in primary care and antimicrobial resistance in patients admitted to hospital with urinary tract infections: a controlled observational pilot. *Antibiotics,* 3:29-38.

Crouch, S., Robinson, P., Pitts, M. 2011. A comparison of general practitioner response rates to electronic and postal surveys in the setting of National STI prevention program. *Australian and New Zealand journal of public health*, 35 (2):187-189.

Crowther-Gibson, P., Govender, N., Lewis, D.A., Bamford, C., Brink, A., Von Gottberg, A., Klugman, K., Du Plessis, M., Fali, A., Harris, B., Keddy, K. H. & Botha, M. 2011. Part IV: Human infections and antibiotic resistance. *South African medical journal*, 101(8). http://www.samj.org.za/index.php/samj/article/view/5102/3367 Date of access: 30 September 2014.

Cunha, A. 2011. Antibiotic essentials. (10th ed). Sudbury, MA: Jones and Bartlett Learning, LLC.

Curtis, B. & Curtis, C. 2011. Social research: a practical introduction. London: SAGE Publication.

Cutts, C. & Tett, S. E. 2003. Influencers on doctors' prescribing: is geographical remoteness a factor? *Australian journal of rural health*, 11:124-130.

Dangor, Y., De Jongh, M., Adam, A. & Hoosen, A. 2010. Antimicrobial susceptibility patterns of gonococcal isolates in Pretoria, South Africa, over a 20 year period (1984-2004). *South African journal of epidemiology and infection*, 25(3):10-13.

Davey, P., Pagliari, C. & Hayes, A. 2002. The patient's role in the spread and control of bacterial resistance to antibiotics. *Clinical microbiology and infection,* 8(2):43-68.

David, M. & Stutton, C..D. 2011. Social research – an introduction. (2nd ed). London: SAGE publications.

Dellit, T.H., Owens, R.C., McGowan, J.E. Jnr., Gerding, D.N., Weinstein, R.A., Burke, J.P., Huskins *et al.* 2007. Infectious Diseases Society of America and the society of Healthcare epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clinical infectious diseases*, 44:159-177.

De Vos, A.S. 2004. Research at grass roots: for the social sciences and human service professions. (2nd ed). Paarl, South Africa: Van Schaik.

Deresinki, S. 2007. Principles of antibiotic therapy in severe infections: optimizing the therapeutic approach by use of laboratory and clinical data. *Clinical infectious diseases*, 45:S177–83.

Desalegn A.A. 2013. Assessment of drug use patterns using the WHO prescribing indicators at Hawassa University teaching and referral hospital, south Ethiopia: a cross sectional study. *BMC health services research,* 13:170.

Dipiro, J., Talbert, R., Yea, G., Matzke, G., Wells, B. & Posey, M. 2008. Pharmacotherapy: a pathophysiological approach. (7th ed). New York: McGraw-Hill Medical.

Djie-Maletz, A., Reither, K., Danour, S., Anyidoho, L., Saad, E., Danikuu, F., Ziniel, P., Weitzel, T., Wagner, J., Bienzle, U., Stark, K., Seidu-Korkor, A., Mockenhaupt, F.P. & Ignatius, R. 2008. High rate of resistance to locally used antibiotics among enteric bacteria from children in Northern Ghana. *Journal of antimicrobial chemotherapy*, 61:1315-1318, March 2008.

Dooling, K., Kandeel, A., Hicks, L.A., El-Shoubary, W., Fawzi, K., Kandeel *et al.* 2014. Understanding antibiotic use in Minya district, Egypt: physician and pharmacist prescribing and factors influencing their practices. *Antibiotics*, 3:233-243.

Dumpis, U., Dimina, E., Akermanis, M., Tirans, E., Veide, S. 2013. Assessment of antibiotic prescribing in Latvian general practitioners. *BMC family practice*, 14:9–13.

Dutta, C. & Pan, A. 2002. Horizontal gene transfer and bacterial diversity. *Journal of biosciences*, 27(1):27–33.

Ebrahim, G.J. 2010. Bacterial resistance to antimicrobials. *Journal of tropical paediatrics*, 56(3):141-143.

Eiselen, R., Uys, T. & Potgieter, T. 2005. Questionnaire design: a workbook. University of Johannesburg, Johannesburg.

Essack, S.Y. 2006. Strategies for the prevention and containment of antimicrobial resistance. *South African family practice,* 48(1):51a-51d.

Essack, Y., Schellack, N., Pople, T., Van der Merwe, L. 2011. Antibiotic supply chain and management in human health. Global antibiotic resistance partnership– situational analysis. Antibiotic use and resistance in South Africa. Part 2. *South African medical journal,* 101(8):562-566.

European Centre for Disease Prevention and Control. 2009. The bacterial challenge: time to react. European Medicines Agency.

Falagas, M.E., Karageorgopoulos, D.E., Lepipdis, J. & Korbilla, I.P. 2013. MRSA in Africa: filling the global map of antimicrobial resistance. *Plos one*, 8(7):e68024 doi:10.1371/journal.pone.0068024

Ferech, M., Coenen, S., Malhotra-Kumar, S., Dvorakova, K., Hendrickx, E., Suetens, C. & Goossens, H. 2006. European surveillance of antimicrobial consumption (ESAC): outpatient antibiotic use in Europe. *Journal of antimicrobial chemotherapy,* 58:401–407. http://jac.oxfordjournals.org/content/58/2/401.long. Date of access: 5 April 2011.

Ferguson, J. 2004. Antibiotic prescribing: how can emergence of antibiotic resistance be delayed. *Australian prescriber*, 27(2):39-42.

Ferver, K., Burton, B. & Jesilow, P. 2009. The use of claims data in healthcare research. *The open public health journal,* 2:11–24.

Finch, R.G. 1998. Antibiotic resistance. *Journal of antimicrobial chemotherapy*, 42:125–128.

Finley, R., Glass- Kaastra, S.K., Hutchinson, J., Patrick, D.M., Weiss, K. & Conly, J. 2013. Declines in outpatient antimicrobial use in Canada (1995–2010). *Plos One,* 8(10):1-7.

Franco, B.E., Martinez, M.A., Rodriguez, M.A. & Wertheimer, I.A. 2009. The determinants of the antibiotic resistance process. *Infection and drug resistance,* 2:1-11.

Fraser, A., Paul, M., Almanasreh, N., Tacconelli, E., Frank, U., Cauda, R., Borok, S., Cohen, M., Andreassen, S., Nielsen, A.D. & Leibovici, L. 2006. Benefit of appropriate empirical antibiotic treatment: thirty-day mortality and duration of hospital stay. *American journal of medicine*, 119:970–976.

Freire-Moran, L., Aronsson, B., Manz, C., Gyssens, I.C., So, A.D., Monnet, D, L. & Carrs, O. 2011. Critical shortage of new antibiotics in development against multidrug-resistant bacteria – time to react is now. *Drug resistance updates,* 14:118–124.

French, G.L. 2005. Clinical impact and relevance of antibiotic resistance. *Advanced drug delivery reviews,* 57:1514–1527.

French, G.L. 2010. Continuing crisis in antibiotic resistance. *International journal of antimicrobial agents,* 36S3:S3–S7.

Furuya, E.Y. & Lowly, F.D. 2006. Antimicrobial-resistant bacteria in the community setting. *Nature reviews: microbiology,* 4:36–45.

G8 UK. 2013. G8 Science Ministers Statement [declaration letter]. 12 June 2013, London, United Kingdom.

Gagliotti, C., Mazetti., I. & Moro., S.L. 2009. Comparison of sales and reimbursement data regarding outpatient antibiotic use in a northern Italian region. *Pharmacoepidemiology and drug safety,* 18:1115–1118.

Gallini, A., Degris, E., Desplas, M., Bourrel, R., Archambaud, M., Montastruc, J., Lapyere-Mestre, M & Sommet, A. 2010. Influence of fluoroquinolone consumption in inpatients and outpatients on ciprofloxacin-resistant *Escherichia coli* in a university hospital. *Journal of antimicrobial chemotherapy,* 65:2650–2657.

Garcia, C., Llamocea, L.P., Garcia, K., Jimonez, A., Samaldives, F., Gotuzzo, E. & Jacobs, J. 2011. Knowledge, attitudes and practice survey about antibiotic prescribing and resistance among physicians in a hospital setting in Lima, Peru. *BMC clinical pharmacology,* 11:18.

Gillings, M.R. 2013. Evolutionary consequences of antibiotic use for the resistome, mobilome, and microbial pangenome. *Frontiers in microbiology*, 4(4):1-10.

Goossens, H. & Sprenger, M.J.W. 1998. Community-acquired infections and bacterial resistance. *British medical journal*, 317: 654–657.

Goossens, H. 2000. Antibiotic resistance and policy in Belgium. *Verhandelingen-Koninklijke Academie voor Geneeskunde van België,* 62:439-469. http://www.ncbi.nlm.nih.gov/pubmed/11144690 Date of access: 3 April 2011.

Goossens, H., Ferech, M., Vander Stichele, R. & Elsiever, M. 2005. Outpatient antibiotic use in Europe and associations with resistance: a cross-national database study. *The Lancet,* 365:579-587.

Goossens, H., Ferech, M., Coenen, S., Stephens, P. & ESAC Project. 2007. Comparison of outpatient systemic antibacterial use in 2004 in the United States with 27 European countries. *Clinical infectious disease,* 44:1091–1095.

Guerra, C.M., Ramos, M.P., Penna, V.Z., Goto, J.M., Santi, L.Q., Stempliuk, V., Sallas, J. & Medeiros, E.A. 2010. Perceptions and attitudes of professional staff about

infection surveillance and control programmes in Brazilian hospitals. *American journal of infection control,* 38:59–62.

Han, K.S.S. & Ramsay, Y. 2013. Surveillance alone plays a key role in curbing the overuse of antimicrobials: the major role of antibiotic stewardship. *South African medical journal*, 103(6):368.

Harbarth, S. & Samore, M.H. 2005. Antimicrobial resistance determinants and future control. *Emerging infectious diseases*, 11(6):794–801.

Hashemi, S., Nasrollah, A. & Rajabi, M. 2013. Irrational antibiotic prescribing – a local issue or a global concern? *Experimental and clinical sciences international journal,* 12:384–395.

Hawkey, P.M. 2008. The growing burden of antimicrobial resistance. *Journal of antimicrobial chemotherapy,* 62(1):i1-19.

Hay, A.D. *et al.* 2005. The relationship between primary care antibiotic prescribing and bacterial resistance in adults in the community: a controlled observational study using inpatient data. *Journal of antimicrobial chemotherapy*, 56:143-156.

Heysell, S.K., Shenoi, S.V., Catterick, K., Thomas, A.T & Friedland, G. 2011. Prevalence of methicillin-resistant *Staphylococcus aureus* nasal carriage among hospital patients with tuberculosis in rural KwaZulu-Natal. *South African medical journal*, 101:332–334.

Hillier, S.L., Magee., J.T., Howard., A.J. & Palmer, S. R. 2002. How strong is the evidence that antibiotic use is a risk factor for antibiotic resistant, community acquired urinary tract infection? *Journal of antimicrobial chemotherapy,* 50:241–257.

Hillier, S., Roberts. Z., Dunstan, F., Buttler, C., Howard, A & Palmer, S. 2007. Prior antibiotic use and risk of antibiotic resistant community acquired urinary tract infection: a case-control study. *Journal of antimicrobial chemotherapy*, 60:92–99.

Holloway, K., Mathai, E. & Gray, E. 2011a. Surveillance of community antimicrobial use in resource constrained settings – experience from five pilot projects. *Tropical medicine and international health,* 16(2):152–161.

Holloway, K., Mathai, E. & Gray, A. 2011b. Community surveillance of antimicrobial use in resource-constrained settings – experience from five pilot projects. *Tropical medicine and international health*, 16(2):152-161.

Howard, D.H., Scott, R.D., Packard, R. & Jones, D. 2003. Global impact of drug resistance. *Clinical infectious disease*, 36(1):S4-S10.

Howard, D.H. 2004. Resistance-induced antimicrobial substitution. *Health economics,* 13(6):585-495.

Hsu, L.Y., Tan, T.Y., Jureen, R., Koh, T.H., Krishnan, P., Lin, R.T.P., Tee, N. W. & Tambyahet, P.A. 2007. Antimicrobial drug resistance in Singapore hospitals. *Emerging infectious disease*, 13(12):1944-1947.

Hsu, L., Tan, T., Tam, V., Kwa, A., Fisher, D. & Koh, T. 2010. Surveillance and correlation of antibiotic prescription and resistance of gram-negative bacteria in Singaporean hospitals. *Antimicrobial agents and chemotherapy,* 54(3):1173-1178.

Hsueh, P., Chen, W. & Luh, K. 2005. Relationship between antimicrobial use and antimicrobial resistance in gram-negative bacteria causing nosocomial infections from 1991-2003 at a university hospital in Taiwan. *International journal of antimicrobial agents,* 26:463-472.

Huang, N., Morlock, L., Lee, C., Chen, L. & Jenq, Y. 2005. Antibiotic prescribing for children with nasopharyngitis (common colds), upper respiratory tract infections and bronchitis who have health professional parents. *Paediatrics,* 116:826–832.

Huang, J.B., Berild, D., Walberg, M. & Reikvam, A. 2011. Increased antibiotic use in Norwegian hospitals despite a low antibiotic resistance rate. *Journal of antimicrobial chemotherapy,* 66:2643–2646.

Hulscher, M.E.J.L., Van der Meer, J.W.M. & Grol, R.P.T.M. 2010. Antibiotics use: how to improve it. *International journal of medical microbiology,* 300:351-356.

Huson, M.A.M., Kalkman, R., Remppis, J., Beyeme, J.O., Kraef, C., Schaumburg, F., Alabi, A.S. & Grobusch, A.P. 2014. Methicillin-resistant *Staphylococcus aureus* as a cause of invasive infection in Central Africa: a case report and review of literature. *Infection*, 42:451–457.

Hutchinson, J.M., Patrick, D.M., Marra, F., Ng, H., Bowie, W.R., Heule, L. Muscat, M. & Monnet, D.L. 2004. Measurement of antibiotic consumption: a practical guide to the use of the anatomical therapeutic chemical classification and defined daily dose system methodology in Canada. *Canadian journal of infectious diseases,* 15(1):29–35.

Huttner, A., Harbarth, S., Carlet, J., Cosgrove, S., Goossens, H., Holmes, A., Jarlier, V., Voss, A. & Pittet, D. 2013. Antimicrobial resistance: a global view from the 2013 World Healthcare-Associated Infections Forum. *Antimicrobial resistance and infection control*, 2:1–13.

Infectious Disease Society of America (IDSA). 2009. Antimicrobial resistance: an escalating threat. http://www.infectiousdiseasenews.com/print.aspx?id=38900). Date of access: 12 March 2011.

International Network for Rational Use of Drugs. http://www.inrud.org/About-INRUD/index.cfm Date of access: 22 October 2012.

Iwalokun, B.A., Gbenle, G.O., Smith, S.I., Ogunledum, A., Akisinde, K. & Omonigbehin, E.A. 2001. Epidemiology of Shigellosis in Lagos, Nigeria: trends in antimicrobial resistance. *Journal of health population and nutrition,* 19(3):183-190, September.

Jaber, L., Peled, T. & Rigler, S. 2004. Antibiotic prescriptions to children with upper respiratory tract infections and bronchitis in Israel. *International journal of risk and safety in medicine*, 16:97–102.

Janssens, W., Gustafsson-Wright, E., De Beer, I. & Van der Gaag, J. 2008. A unique low-cost private health insurance program in Namibia: protection from health shocks including HIV/AIDS. *International institute of social studies*. http://www.iss.nl/DevISSues/Articles/A-Unique-Low-cost-Private-Health-Insurance-Program-in-Namibia-Protection-from-Health-Shocks-Including-HIV-AIDS Date of access: 5 July 2010.

Jaruseviciene, L., Jurgute, R.R., Bjerum, L., Jurgutis, A., Jarusevicius, G. & Lazarus, J.V. 2013 Enabling factors for antibiotic prescribing for upper respiratory tract infections: perspectives of Lithuanian and Russian general practitioners. *Upsalla journal of medicine*, 118:98–104.

Jensen, U.S., Muller, A., Brandt, C.T., Fridmodt-Møller, N., Hammerum, A.M. & Monnet D.L. 2010. Effects of generics on price and consumption of ciprofloxacin in primary healthcare: a relationship to increasing resistance. *Journal of antimicrobial chemotherapy,* 65:1286–1291.

Jonas, A., Gweshe, J., Sibolokela, M., De Klerk, M., Gawanab, M., Badi, A., Sumbi, V., Pereko, D., Blom, A., Mwinga, S., Jordan, M.R., Jerger, M.R., Lau, K., & Hong, S.Y.

2013. HIV drug resistance early warning indicators in Namibia for public health action. *Plos One*, 8 (6): e65653. doi: 10.1371/journal.pone.0065653

Jose, J., Jimmy, B., AlSabahi, S. & Al Sabei, A. 2013. A study assessing public knowledge, belief and behaviour of antibiotic use in an Omani population. *Omani medical journal,* 28(5):324–330.

Kamal., K.M. 2011. Operationalizing research. (In Aparau, R. ed. Research methods for pharmaceutical practice and policy. London : Pharmaceutical press, 37-52.)

Katzenellenbogen J.M., Joubert, G. & Yach, D. 2004. Epidemiology: a manual for South Africa. Cape Town, Oxford University Press.

Kaufman, G. 2011. Antibiotics: mode of action and mechanisms of resistance. *Nursing standard*, 25 (42): 49 – 55.

Kellerman, S. E. & Harold. J. 2001. Physician's response to surveys: a review of literature. *American journal of preventative medicine*, 20(1):61–67.

Kheder, S.I. & Ayed. I.A. 2013. A survey of public knowledge and behaviour related to antibiotic use and resistance in community pharmacies in Khartoum state. *International journal of bioassay*, 2(5):751–755.

Kheder, S.I. 2014. Physicians knowledge and perception of antimicrobial resistance: a survey in Khartoum state hospitals settings. *British journal of pharmaceutical research,* 3(3):347–362.

Kibret, M. & Abera, B. 2011. Antimicrobial susceptibility patterns of E-coli from clinical sources in northern Ethiopia. *African health sciences*, 11(1):S40-S45.

Kim, S.S., Moon, S. & Kim, E.J. 2011. Public knowledge and attitudes regarding antibiotic use in South Korea. *Journal of Korean academy of nursing,* 6:742-749.

Kimang'a, A.N. 2012. A situational analysis of antimicrobial drug resistance in Africa: are we losing the battle? *Ethiopian journal of health sciences,* 22(2):135–143, July 2012.

Kinge, C. N. W., Ateba, C. N. & Kawadza, D. T. 2010. Antibiotic resistance profiles of Escherichia coli isolated from different water sources in the Mmabatho locality, north-west province, South Africa. *South African journal of science,* 106(1-2): 44-49, February.

Klugman, K.P. 1998. Emerging infectious diseases- South Africa. *Emerging infectious diseases,* 4(4): Oct-Dec. http://wwwnc.cdc.gov/eid/article/4/4/98-0401_article.htm Date of access: 6 January 2012.

Knobler, S.L., Lemon, S.M., Najafi, M. & Burroughs, T. 2003. The resistance phenomenon in microbes and infectious disease vectors: Implications for human health and strategies. National Academy Press. http://www.nap.edu/openbook.php?record_id=10651&page=20 Date of access: 20 October 2012.

Kollef, M.H. 2000. Inadequate antimicrobial treatment: an important determinant of outcome for hospitalized patients. *Clinical infectious disease*, 31(4):S131–S138.

Kotwani, A., Holloway, K. & Chaudhury, R.R. 2009. Methodology for surveillance of antimicrobial use among outpatient in Delhi. *Indian journal of medical research*, 129:555–560.

Kotwani, A. & Holloway, K. 2011. Trends in antibiotic use among outpatients in New Delhi, India. *BMC infectious disease,* 11:99–107.

Kotwani, A., Wattal, C, Joshi. P.C. & Holloway, K. 2012. Irrational use of antibiotics and role of pharmacist: an insight from a qualitative study in New Delhi, India. *Journal of clinical pharmacy and therapeutics,* 37:308–312.

Kouyaté, B., Sie, A., Yé, M., De Allegri, M. & Müller, O. 2007. The great failure of malaria control in Africa: A district perspective from Burkina Faso. *Public library of science medicine,* 4(6): e127(997-1000).

Kritsotakis, E.I., Christidou, A., Roumbelaki, M., Tselentis, Y. & Gikas, A. 2008. The dynamic relationship between antibiotic use and the incidence of vancomycin-resistant Enterococcus: time series modelling of 7 years surveillance data in a tertiary care hospital. *Clinical microbiology and infection,* 14:747-754.

Kwint, H.M., Van der Linden, P.D., Roukens, M.M.B. & Natsch, S. 2012. Intensification of antibiotic use within acute care hospitals in the Netherlands. *Journal of antimicrobial chemotherapy*, 67:2283–2288.

Lai, C. *et al.* 2011. Correlation between antibiotic use and resistance of gram-negative bacteria causing healthcare-associated infections at a university hospital in Taiwan from 2000-2009. *Journal of antimicrobial chemotherapy*, 66:1374-1382.

Lancet Infectious Disease Commission. 2013. Antibiotic resistance – the need for global solutions. *Lancet,* S1473-3099 (13)70318-9.

Larson, E. 2007. Community factors in the development of antibiotic resistance. *Annual review of public health,* 28:435– 447.

Lates, J. 1999. Study of antibiotic prescribing habits in clinics in Directorate: Central Region. Ministry of Health and Social Services.

Lates, J. & Shiyandja, N. 2001. 3rd National survey on the use of drugs in Namibia's public health institutions including monitoring the implementation of the National Drug Policy. Ministry of Health and Social Services.

Lawrence, J.G. 2005. Horizontal and vertical gene transfer: the life history of pathogens. *Concepts in bacterial virulence*, 12:255–271.

Laxminarayan, R. & Heymann, D. 2012. Challenges of drug resistance in the developing world. *British medical journal*, 344:e1567 doi: 10.1136/bmj.e1567

Lee, C.G., Reveles, K.R., Attridge, R.T., Lawson, K.A., Mansi, I.A., Lewis II, J.S., Frei, C.R. 2014. Outpatient antibiotic use in the United States: 2000-2010. *BMC Medicine*, 12:96 doi: 10.1186//1741-7015-12-96

Leekha, S., Terrell, C.L. & Edson, R.S. 2011. General principles of antimicrobial therapy. *Mayo Clinic proceedings*, 86(2):156-167.

Leung, E., Weil, D., Raviglione, M. & Nakatani, H. 2011. Policy package to combat antimicrobial resistance. *Bulletin World Health Organization,* 89:390–392.

Levin, S.A. & Andreasen, V. 1999. Disease transmission dynamics and the evolution of antibiotic resistance in hospitals and communal settings. Proceedings of *national academy of science,* 96:800-801. February 1999.

Levy, S.B. 1998. The challenge of antibiotic resistance. *Scientific American*, 46-53, March 1998.

Levy, S.B. 2002. Factors impacting on the problem of antibiotic resistance. *Journal of antimicrobial chemotherapy*, 49:25-30.

Levy, S.B. 2003. Antibiotic resistance 1992–2002: a decade journey. (In *the resistance phenomenon in microbes and infectious disease vectors: implications for human health*

and Strategies for Containment -- Workshop Summary). The National Academies Press. Washington: DC, 32-43.

Levy, S.B. & Marshall, B. 2004. Antibacterial resistance worldwide: causes, challenges and responses. *Nature medicine supplement*, 10(12) S122–S129.

Levy, S.B. 2005. Antibiotic resistance – the problem intensifies. *Advanced drug delivery review,* 57:1446–1450.

Lewis, D. 2002. Antimicrobial resistance surveillance: methods will depend on objectives. *Journal of antimicrobial chemotherapy*, 49(1):3-5.

Lewis, D.A. 2011. Antimicrobial resistant gonorrhea in Africa: an important public health threat in need of a regional gonorrheal antimicrobial surveillance programme. *Southern African journal of epidemiology and infection*, 26 (4): 215 – 220.

Lima, A.P., Gallani, N.R., De Toledo, M.I. & Lopes, L.C. 2008. Uses of Pharmacy Benefit Management (PBM) system to describe the profile of prescription and purchases. Abstract. *Brazilian journal of pharmaceutical sciences,* 44: 215-223.

Lipsitch, M., Bergstrom, C.T. & Levin B. R. 2000. The epidemiology of antibiotic resistance in hospitals: paradoxes and prescriptions. *Proceedings of the National Academy of Sciences of the United States of America,* 90(4):1938–1943.

Llor, C. & Cots, J.M. 2009. The sale of antibiotics without prescription in pharmacies in Catolina, Spain. *Clinical infectious disease,* 48:1345–1349.

Low, M., Nitzan, O., Bitterman, H., Cohen, C., Hammerman, C., Lieberman, N. *et al.* 2013. Trends in outpatient antibiotic use in Israel during the years 2000 – 2010: setting targets for an intervention. *Infection*, 41:401-407.

Lucet, J., Nicolas-Chanoine, M., Roy, C., Riveros-Palacios, O., Diamantos, S., LeGrand, J., Popy, E., Rioux, C., Fantin, B., Lefort, A. & Ravaud, P. 2011. Antibiotic use- knowledge and perceptions in two university hospitals. *Journal of antimicrobial chemotherapy,* 66:936–940.

MacGowan, A.P. 2008. Clinical Implications of antimicrobial resistance for therapy. *Journal of antimicrobial therapy*, 62(2):ii105–ii 114

Magee, J.T., Pritchard, E.L., Fitzgerald, K.A., Dunstan, F.D. & Howard, A.J. 1999. Antibiotic prescribing and antibiotic resistance in community practice: retrospective study, 1996–8. *British medical journal,* 319:1239-1240. http://www.bmj.com/content/319/7219/1239.1.full Date of access: 25 March 2012.

Malhotra-Kumar, S., Lammens, C., Coenen, S., Van Herck, K. & Goossens, H. 2007. Effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers: a randomised, double-blind, placebo controlled study. *Lancet*; 369:482-490.

Management Sciences for Health: Strengthening Pharmaceutical Systems. 2008. *How to investigate antimicrobial use in hospitals: selected Indicators.* Arlington, VA.

Mandomando, I., Jaintilal, D., Pons, M.A., Valles, X., Espasa, M., Mensa, L., Segauque, B., Sanz, S., Sacarlal, J., Macete, E., Abacassamo, F., Alfonzo, L.P. & Ruiz. J. 2009. Antimicrobial susceptibility and mechanisms of resistance in Shigella and Salmonella isolates in children under five years of age with diarrhea in rural Mozambique. *Antimicrobial agents and chemotherapy*, 53(6):2450-2454.

Mann, C.J. 2003. Observational research methods. Research design II: cohorts, cross sectional and case control studies. *Emergency medical journal,* 20:54-60.

Maree, K. 2010. First steps in Research. Pretoria, Van Schaik.

Marias, E., Arthma, N., Perovic, O., Oosthuizen, W.F., Musenge, E & Duse, A.G. 2009. Antimicrobial susceptibility of methicillin-resistant staphylococcus aureus isolates from South Africa. *South African medical journal,* 99(3):170-173.

Marks, S., Flood, J., Seaworth, B., Hirsch-Movermon, Y., Armstrong, L., Mase, S., Salcedo, K., Oh, P., Graviss, E.A., Colson, P.W., Armitige, L., Revuelta, M., Sheeran, K., & The TB Epidemiologic Studies Consortium. 2014. Treatment practices, outcomes and costs of multidrug- resistant and extensively drug resistant- tuberculosis, United States, 2005-2007. *Emerging infectious diseases*, 20(5):812–820.

Masterton, R. 2008. The importance and future of antimicrobial surveillance studies. *Clinical infectious disease,* 47(1)S21-S31.

McNulty, A.M., Boyle, P., Nichols, T., Clappison, P. & Davey, P. 2007a. The public's attitude to and compliance with antibiotics. *Journal of antimicrobial chemotherapy*, 60 (1):i63–i68.

Medicines and Related Substances Control ***see*** Namibia

MediKredit Integrated Healthcare Solutions. 2014. National Pharmaceutical Product Index (NAPPI) product suite. Author. **https://www.medikredit.co.za** Date of access: 8 March 2014.

Mehta, M., Bhardwaj, S. & Shorma, J. 2012. Prevalence of antibiotic susceptibility patterns of multi-drug resistant Escherichia Coli isolates from urinary tract infections (UTI) patients. *International journal of life science and pharma research*, 2 (4):L6–L11.

Mengistu, A. 2012. Functions of the Therapeutic Information and Pharmacovigilance Center (TIPC) [personal interview]. 29 October 2012, Windhoek.

Ministry of Health and Social Services ***see*** Namibia. Ministry of Health and Social Services.

Mir, F. & Zaidi, A.K.M. 2010. Hospital infections by antimicrobial resistant organism (In Okeke,I & Sosa, *A. Antimicrobial resistance in developing countries*. New York: Springer, 248-249.)

Mitsi, G., Jelastopulu, E., Basiaris, H., Skoutelis, A. & Gogos, C. 2005. Patterns of antibiotic use among adults and parents in a community: a questionnaire based survey in a Greek urban population. *International journal of antimicrobial agents,* 25:439-443.

Mohamat, A., Lavigne, J.P., Fabro-Perray, P., Kinowski, J.M., Duares, J.P. & Sotto, A. 2005. Evolution of fluoroquinolone resistance among *Escherichia coli* urinary tract isolates from a French university hospital: application of the dynamic regression model. *Clinical microbiology and infection,* 11:301-306.

Mohamed, H. F., Alanizy, N., Almutairi, S., Alshamari, E. & Akelly, H. 2014. Patterns, knowledge and attitudes of irrational antibiotic use in Saudi community. *Journal of biology, agriculture and healthcare,* 4(4):74–77.

Mollahaliloglu, S., Alkan, A., Dornetas, B., Ozgulcu, S. & Akici., A. 2012. Assessment of antibiotic prescribing at different hospitals and primary health care facilities. *Saudi pharmaceutical journal,* 21:281–291.

Moodley, P., Pillay,C., Goga, R., Kharsany, A.B. & Sturm, W. 2001. Evolution in trends of antimicrobial resistance in Neisseria gonorrhoeae isolated in Durban over a 5 year period: impact of the introduction of syndromic management. *Journal of antimicrobial therapy*, 48:853–859.

Morgan, D.J., Okeke, I.N., Laxminarayan, R., Perenevich, E.N. & Weisenberg, S. 2011 Non-prescription antimicrobial use worldwide: a systemic review. *Lancet Infectious Disease,* 11:692-701.

Mouton, J. 2002. Understanding social research. Pretoria, Van Schaik.

Mulvey, M & Simor, A. 2009. Antimicrobial resistance in hospitals: how concerned should we be? *Canada medical association journal,* 180(4):408-415.

Munckhof, W. 2005. Antibiotics for surgical prophylaxis. *Australian prescriber*, 28(2):38–40.

Murray, B.E. 1991. New aspects of antimicrobial resistance and the resulting therapeutic dilemmas. *The journal of infectious diseases,* 163(6):1185–1194. http://jid.oxfordjournals.org/content/163/6/1185.short Date of access: 14 February 2011.

Murphy, M., Bradley, C.P., Byrne, S. 2012. Antibiotic prescribing in primary care, adherence to guidelines and unnecessary prescribing – an Irish perspective. *BMC family practice,* 13:43.

Muvunyi, C.M., Masaisa, F., Bayingana, C., Mutesa, L., Musemakweri, A., Muirwa, G. & Claeys, G. 2011. Decreased susceptibility to commonly used antibacterial agents in pathogens isolated from the urinary tract infections in Rwanda: need for new antimicrobial guidelines. *American journal of tropical medicine and hygiene*, 84(6):923-928.

Nagaraj, S., Chandran, S.P., Shamann, P. & Macaden, R. 2012. Carbapenem resistance among Escherichia coli and Klebsiella pneumoniae in a tertiary care hospital in south India. *Indian journal of medical microbiology*, 30:93-95.

Namibia. 1994. Hospital and Health Facilities Act 36 of 1994

Namibia. 2003. Medicines and Related Substances Control Act 13 of 2003.

Namibia Medicines and Regulatory Council (NMRC). www.nmrc.com.na

Namibia. Ministry of Health and Social Services. 2005. Equity in health care in Namibia: towards needs based allocation formula. Windhoek: Author

Namibia. Ministry of Health and Social Services [Namibia] and Health Systems 20/20 [Bethesda]. 2008a. *Namibia National Health Accounts 2001/02–2006/07*. Windhoek & Bethesda, MD, USA: Health Systems 20/20 project, Abt Associates Inc.

Namibia. Ministry of Health and Social Services (Namibia) and Macro International Inc. 2008b. *Namibia demographic and health survey 2006/07*. Windhoek.

Namibia. Ministry of Health and Social Services. 2008c. *Health and social services systems review*. Windhoek: Author.

Namibia. Ministry of Health and Social Services. 2008d. *Namibia Essential Medicines List* (Nemlist).(4th ed.). Windhoek: Author.

Namibia. Ministry of Health and Social Services [Namibia] and ICF Macro. 2010a. *National health facility census 2009*. Windhoek.

Namibia. Ministry of Health and Social Services. 2010b. *National health policy framework,* 2010–2020. Windhoek: Author. July 2010.

Namibia. Ministry of Health and Social Services. 2010c. *Namibia health and HIV/AIDS resource tracking*:2007/08 & 2008/09. Windhoek: Author. July 2010.

Namibia. Ministry of Health and Social Services. 2011a. *National medicines policy*, (2nd ed.). Windhoek, Author.

Namibia. Ministry of Health and Social Services. 2011b. *National guidelines for medicines safety surveillance*. Windhoek: Author. November 2011.

Namibia. Ministry of Health and Social Services. 2011c. *Namibia standard treatment guidelines*. Windhoek: Author.

Namibia. National Planning Commission. 2010. 2006 Namibia Inter census demographic survey. http://www.npc.gov.na/publications/census_data/NIDS_report_final_revised_04%20August%202010.pdf.Date of access: 17 September 2012.

Namibia. National Planning Commission. 2012. Namibia 2011 population and housing census. Windhoek. April 2012.

Napolitano, F. Izzo, M.T. Di Giuseppe, G. & Angelillo, I.F. 2013. Public knowledge, attitude and experience regarding the use of antibiotics in Italy. *Plos One* 8 (12):e84177.

National Institute of Allergy and Infectious Diseases (NIAID). 2011. Antimicrobial resistance. http://www.niaid.nih.gov/topics/antimicrobialResistance/Understanding/drugResistanceDefinition.htm Date of access: 23 March 2011.

National Institute of Communicable Diseases. 2013. Update on carbapenemase-producing enterobacteriaceae (CPE). *Communicable diseases communiqué*, 12(11):6–16.

Nelson, N., Moshi., M. & Kirika, J. 2009. *Antimicrobial resistance: the need for action in the east, central and southern Africa region. Strengthening pharmaceutical systems, Management Sciences for Health*. Arlington, Virginia.

Neuman, W. 2014. Social research methods: qualitative and quantitative approaches. 7th ed. Pearson Education Limited, Harlow.

Nichols, K., Chapman, K., Shaw, T., Perkins, A., Murray Sullivan, M., Crutchfield, S. & Reed. E. 2011. Enhancing response rates in physician surveys: the limited utility of electronic options. *Health services research,* 46 (5): 1675 – 1682.

Nicolau, D. (2002). Clinical and economic implications of antimicrobial resistance in the management of community-acquired respiratory tract infections. *Journal of antimicrobial chemotherapy,* 50(S1): 61 -70.

Nicolle, L. 2003. Forum on emerging infections. Factors contributing to the emergence of resistance. (In *the resistance phenomenon in microbes and infectious disease vectors: implications for human health and strategies for containment -- workshop summary)*. The National Academies Press. Washington, DC, 130-158.

Nordmann, P., Cuzan, G. & Naas, T. 2009. The real threat of Klebsiella pneumoniae carbapenemase-producing bacteria. *Lancet infectious disease*, 9:228-236.

Ntšheke, M., Hoohlo-Khotle, N., Tlali, M & Tjipura, D. 2011. Antibiotic prescribing patterns at six hospitals in Lesotho. *Management Sciences for Health,* Arlington, VA.

Nunes, V., Nielson, J., O'Flyn , N., Calvert, N., Kuntze, S., Smithson, H., Benson, J., Blair, J., Bowser, A., Clyme, W., Crome, P., Haddad, P., Hemmingway, S., Horn, R., Johnson, S., Kelly, S., Packham, B., Patel, M. & Steele, J. 2009. Clinical guidelines and evidence review for medicines adherence: involving patients in decisions and prescribed medicines and supporting adherence. *National collaborating centre for primary care and royal college of general practitioners, London*.

Nyasulu, P., Murray, J., Perovic, O. & Koornhof, H. 2012. Antimicrobial resistance surveillance among nosocomial pathogens in South Africa: systemic review of published literature. *Journal of experimental and clinical medicine,* 4 (1): 8–13.

Obi, C.L., Potgieter, N., Bessong, P.O., Igumbor, E.O. & Green, E. 2003. Prevalence of pathogenic bacteria and retroviruses in stools of patients presenting with diarrhoea from rural communities in Venda, South Africa. *South African journal of science*, 99:589–592.

O'Hanlon, B., Feely, F., De Beer, I., Sulzbach, S. & Vincent, H. 2010. Namibia private sector assessment. Bethesda, MD: strengthening health outcomes through private sector. Abt Associates Inc.

Oh, A. I., Hassali, M.A., Al-Haddad, M. S., Sulaiman, S., Shafie, A.A. & Awaisu, A. 2011. Public knowledge and attitude towards antibiotic usage: a cross-sectional study among the general public in the state of Penang, Malaysia. *The journal of infection in developing countries*, 5(5): 338-347.

Ojulong, J., Mwambu, T.P., Joloba, M., Bwanga, F. & Kaddu-Mulindwa, D.H. 2009. Relative prevalence of methicillin-resistant staphylococcus aureaus and its susceptibility patterns in Mulago Hospital, Kampala, Uganda. *Tanzania journal of health research* 11(3):149–153, July 2009.

Okeke, I.N., Lamikanra, A.,& Edelman, R. 1999. Socioeconomic and behavioral factors leading to acquired bacterial resistance to antibiotics in developing countries. *Emerging infectious diseases,* 5(1):18-27.

Okeke, I.N., Fayihka, S. T. & Lamikanra, A. 2000. Antimicrobial resistance in Escherichial coli in Nigerian students, 1986–1998. *Emerging infectious diseases,* 6(4):393-396, August.

Okeke, I.N., Klugman, K.P., Bhutta, Z.A., Duse, A.C., O'Brien, T.F., Pablo-Mendez, A. & Laxminarayan, R. 2005. Antimicrobial resistance in developing countries part II: strategies for containment. *Lancet infectious diseases*, 5:568–580.

Okeke I.N., Aboderin, O.A., Byarugaba, D.K., Ojo, K. & Opniten, J. 2007. Growing problem of multi-drug resistant enteric pathogens in Africa. *Emerging infectious diseases*, 13(11):1640–1646.

Okeke, N., Laxminarayan, R., Bhutta, Z., Duse, A., Jenkins, P., O'Brien,T., Pablos-Mendez, A. &K. 2005. Antimicrobial resistance in developing countries. Part I: recent trends and current status. *The Lancet*, 5(8):481-493, August. http://www.thelancet.com/journals/laninf/article/PIIS1473-3099 (05)70189-4/fulltext. Date of access: 16 March 2009.

Okeke, N. & Sosa, A. 2008. Antibiotic resistance in Africa – discerning the enemy and plotting a defense.

Orsi, G.B., Falcone, M. & Venditti, M. 2011. Surveillance of management of multidrug resistant microorganisms. *Medscape*. http://www.medscape.com/viewarticle/754322 Date of access: 26 January 2011.

Paluck, E., Katzenstein, D., Frankish, C.J., Hebert, C.P., Milner, R., Speert, D. & Chambers, K. 2001. Prescribing attitudes and practices towards giving children antibiotics. *Canadian family physician,* 47:521–527.

Paterson, D. 2006. Maximizing therapeutic success in an era of increasing antibiotic drug resistance**.** *Medscape*. www.medscape.org/viewarticle/530787 Date of access: 8 November 2009.

Parimi, N., Pereira, L. & Prabhakar, P. 2002. The general public's perceptions and use of antimicrobials in Trinidad and Tobago. *Pan American journal of public health*, 12(1):11–17.

Pechere J.C. 2001 . Patient's interviews and misuse of antibiotics. *Clinical infectious disease*, 33(3):S170–S173.

Pendleton, J.N., Gorman, S.P. & Gilmore, B.F. 2013. Clinical relevance of the ESKAPE pathogens. *Medscape,* 11(3):297-308. http://www.medscape.com/viewarticle/780768. Date of access: 9 September 2013.

PEPFAR/NAMIBIA. 2011. Namibia Global Health Initiative 2011-2015/16. Windhoek,

Perry, I.D., Nagvi, S. H., Miza, I. A., Alizia, S.A., Hussain, A., Ghirardi, S., Orenja, S., Wilkinson, R., Woodford, N., Zhang, J., Livemore, D.M., Abbasi, S.A & Reza, M.W. 2011. Prevalence of faecal carriage of enterobacterifaceae with NDM-1carbapenemase at military hospitals in Pakistan and evaluation of two chromogenic media. *Journal of antimicrobial chemotherapy*, 66 :2288-2294.

Petersen, I. & Hayward, A.C. 2007. Antibiotic prescribing in primary care. *Journal of antimicrobial chemotherapy,* 60(1):i43– i47.

Pflomm, J. 2002. Strategies for minimizing antimicrobial resistance. *American journal of health systems pharmacy*, 59(3):S12–S15.

PharmAccess Foundation Namibia. 2011. The Okambilibili health insurance project in Namibia: great stories and lessons learnt. March 2011.

Phulu, B., Sumbi, V., & Lates, J. 2012. 18th National PMIS feedback report covering data submitted for April 2011 to March 2012. *Feedback Report to Regions, MoHSS, Division: Pharmaceutical Services, Windhoek.*

Pit, S.W., Vo, T. & Pyakurel, S. 2014. The effectiveness of recruitment strategies on general practitioners' survey response rate – a systemic review. *BMC medical research methodology* ,14:76.

Pooran, A., Pieterson, E., Davids, M., Theron, G. & Dheda, K. 2013. What is the cost of diagnosis and management of drug resistant tuberculosis in South Africa? *PlosOne,* 8(1):e54587.

Powers, J.H., Phoenix, J.A. & Zuckerman, D.M. 2010. Antibiotic uses and challenges - a comprehensive review from NRCWF. *Medscape*.
www.medscape.com/viewarticles/723457 Date of access: 26 March 2013.

Pulcini, C., William, F., Molinari, N., Davey, P. & Nathwani, D. 2011. Junior doctors' knowledge and perception of antibiotic resistance and prescribing – a survey in France and Scotland. *Clinical microbiology and infection,* 17:80-87.

Radkhakrishma, R.B. 2007. Tips for developing and testing questionnaire/instruments. *Journal of extension,* 45(1). www.joe.org/joe/2007february/tt2php Date of access: 5 March 2013.

Radyowajati, A. & Haak, H. 2002. Determinants of antibiotic use in developing world. *Child health research project special report*; 4(1):1–39.

Raghunath, D. 2008. Emerging antibiotic resistance in bacteria with special references to India. *Journal of bioscience,* 33(4):593-603.

Raji, M.A., Jamal, W., Ojemhen, O. & Rotimi, V.O. 2013. Point surveillance of antibiotic resistance in Enterobacteriaceae isolates from patients in a Lagos teaching hospital, Nigeria. *Journal of infection and public health*, 6:431-437.

Randrianirina, F., Vaillant, L., Ramarokoto, C.E., Rakotoarijaona, A., Andriamanarivo, M.L., Razafimahandry, H.C., Randrianomenjanahary, J., Raveloson, J.R., Hariniaina, E.R., Carod, J., Talarmin, A., & Richard, V. 2010. Antimicrobial resistance in pathogens causing nosocomial infections in surgery and intensive care wards in Antananarivo, Madagascar. *Journal of infections in developing countries*, 3(4):74–82.

Raz, R., Hefter, H., Oren, B., Kennes, Y., & Potasman, I. 1993. Antimicrobial resistance of urinary isolates in the community and its relation to antibiotic use. *Israel journal of medical sciences,* 29:207–210.

Reda, A.A., Seyoum, B., Yimam, J., Andualem, G., Fiseha, S. & Vandeweerd, J. 2011. Antibiotic susceptibility patterns of *Salmonella* and *Shigella* in Hara, Eastern Ethiopia. *Journal of infectious diseases and immunity*, 3(8):134-139.

Rhada, L. & Trivedi, M.J. 2015. Utilization of online survey tools for academic research: a practical approach to Survey Monkey. Research journal of science and IT management, 4 (3): 21 – 28.

Rice, L.B. 2008. Federal funding for the study of antimicrobial resistance in nosocomial pathogens: no ESKAPE. *The journal of infectious diseases,* 197:1079–1081.

Ringertz, S. & Kronvall G. 1987. Increased use of erythromycin causes resistance in Haemophilus influenzae. *Scandanavian Journal of infectious diseases,* 19:247-256. (Abstract). http://informahealthcare.com/doi/abs/10.3109/00365548709032407 Date of access: 16 March 2011.

Roberts, R.R., Hota, B., Ahmad, J., Scott II, D.R., Foster, S.D., Abbasi, F., Schabowski, S., Kampe, L.M., Ciavarella, G.G., Supino, M., Naples, J., Cordell, R., Levy, S.B. & Weinstein, R.A. 2009. Hospital and societal costs of antimicrobial-resistant infections in a Chicago teaching hospital: implications for antimicrobial stewardship. *Clinical infectious disease*, 49:1175-1184.

Rodriguez, A.T., Roque, F., Falcão, A., Figueiras, A., & Herdeiro, M.T. 2013. Understanding physician antibiotic prescribing behaviour: a systemic review of qualitative studies. *International Journal of antimicrobial agents*, 41:203-212.

Rousounidis, A., Papaevangelou, V., Hadijipanayis, A., Pangakou, S., Theodoridou, M., Syrogiannopoulos, G. & Hadjichristodoulou, C. 2011. Descriptive study on parents' knowledge, attitudes and practices on antibiotic use and misuse in children with upper respiratory tract infection in Cyprus. *International journal of environmental research and public health,* 8:3246–3262.

Saamstamoinen, L., Enlund, H. & Klaukka T. 2008. Repeat prescription in primary care: a prescription study. *Pharmacy world and science journal*, 30: 605-609, May.

Sabry, N.A., Ferid, S.F., Dawoud, D.M. 2014. Antibiotic dispensing in Egyptian community pharmacies: an observational study. *Research in social and administrative pharmacy*, 10:168–184.

Saleem, A. F., Ahmed, I., Mir, F., Ali, S.R. & Zaid, A.K.M. 2010. Pen resistant *Acinetobacter* infection in neonates in Karachi, Pakistan. *The journal of infection in developing countries*, 4 (1): 30 -37.

Saleem, A.F., Qamar, F.N., Shahizad, H., Qadir, M. & Zaidi, A.K.M. 2013. Trends in antibiotic susceptibility and incidence of late-onset *Klebsiella pneumonia* neonatal sepsis over a six year period in neonatal intensive care unit in Karachi, Pakistan. *International journal of infectious diseases*, 17:e961–e965.

Schechner, V., Temkin, E., Harbarth, S., Carmeli, Y. & Schwaber, M. 2013. Epidemiological interpretation of studies examining the effect of antibiotic use on resistance. *Clinical microbiology reviews*, 26(2):289-307.

Seppala, H., Klaukka, T., Lehtonen, R., Nenonen, E. & Huovinen, P. 1995. Outpatient use of erythromycin: link to increased erythromycin resistance in group A streptococci. *Clinical infectious disease,* 21: 378–1385. (Abstract). http://cid.oxfordjournals.org/content/21/6/1378.short Date of access: 25 March 2011.

Seppala, H., Klaukka, T., Vuopio-Varkila, J., Muotiala, A., Helenius, H., Lager, K. & Huovinen, P. 1997. The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococci in Finland. Finnish Study Group for Antimicrobial Resistance. *New England journal of medicine,* 337:441–446. http://www.ncbi.nlm.nih.gov/pubmed/9250845 Date of access: 25 March 2011.

Shaban, R.Z., Cruickshank, M. & Christainsen, K. 2012. National surveillance and reporting of antimicrobial resistance and antibiotic usage in Australia. Australian commission on quality and safety in health care. Sydney.

Shahid, M., Malik, A., Akram, M, Agrawal, L.M., Khan, A.U. & Agrawal. M. 2008. Prevalent phenotypes and antibiotic resistance in Escherichia coli and Klebsiella pneumonia at an Indian tertiary hospital: plasmid-mediated cefoxitin resistance. *International journal of infectious diseases*, 12:256–264.

Shehadeh, M., Suiafan, G., Darwish, R. M., Wazaify, M., Zaru, L. & Alja'fari, S. 2012. Knowledge, attitudes and behaviour regarding antibiotics use and misuse among adults in the community of Jordan. A pilot study. *Saudi pharmaceutical journal,* 20:125–133.

Shuttleworth, M. 2009. Validity and reliability. https://explorable.com/types-of-validity Date of access: 12 March 2014.

SIGN (Scottish Intercollegiate Guidelines Network). 2008. Antibiotic prophylaxis in surgery: A national clinical guideline.

Simonsen, G.S., Tapsall, J.W., Allegranzi, B., Talbot, E.A. & Lazzari, S. 2004. The antimicrobial resistance containment and surveillance approach – a public health tool. *Bulletin of the World Health Organization*, 82(12): 928–934.

Sirinavin, S. & Dowell, S.F. 2004. Antimicrobial resistance in countries with limited resources: unique challenges and limited alternatives. *Seminars on pediatric infectious disease*, 15(2):94-98.

Skjøt-Rasmussen, L., Olsen, S.J. & Jensen, US 2012. Increasing consumption of antimicrobial agents in Denmarkparallels increasing resistance in *Escherechia coli* bloodstream isolates. *International journal of antimicrobial agents,* 40:86–88.

Skliros, E., Merkouris, P., Ppazafiropolou, A., Gikas, A., Matzouranis, G., Papafiragos, C., Tsakanikas, I., Zarbala, I., Vasibosis, A., Stamataki, P. & Sotiropoulos, A. 2010. Self-medication with antibiotics in a rural population in Greece: a cross-sectional multicentre study. *BMC family practice,*11:58.

Smith, A.M., Keddy, K.H. & De Wee, L. 2008. Characterization of cholera outbreak isolates from Namibia, December 2006 to February 2007. *Epidemiology and infection*, 136:1207–1209. (Abstract).

Sosa, A., Byarugaba, D., Amábile-Cuevas, C., Hsueh, P., Kariuki, S. & Okeke, I. 2010. Antimicrobial resistance in developing countries. Springer, New York.

South Australian Infection Control Services. Antimicrobial surveillance. http://www.health.sa.gov.au/INFECTIONCONTROL/Default.aspx?tabid=198. Date of access: 25 May 2013.

Spellberg, B., Guidos, R., Gilbert, D., Bradley, J., Boucher, H.W., Scheld, M., Bartlett., J.G. & Edwards, J. (for IDSA). The epidemic of antibiotic-resistant infections: a call to action for the medical community from the Infectious Disease Society of America. *Clinical infectious disease,* 46:155–164.

Stach, L.M., Hedican, E.B., Herigon, J.G., Jackson, M.A. & Newland, J.S. 2012. Clinicians' attitudes towards an antimicrobial stewardship program at a children's hospital. *Journal of the paediatric infectious diseases society*, 1(3):190–197.

Stein, C., Weber, D. & Kelley, M. 2003. Using hospital antibiogram data to assess regional pneumococcal resistance to antibiotics. *Emerging infectious diseases,* 9 (12):211 – 216.

Steinke, D. and Davey, P. 2001. Association between antibiotic resistance and community prescribing: a critical review of bias and confounding in published studies. *Clinical infectious disease*, 33(3):S193–S205.

Stille, J.C., Andrade, S.E., Huang, S., Nordin, J., Raebel, M., Go, A., Chan, A & Finkelstein, J. 2004. Increased use of second-generation macrolide antibiotics for children in nine health plans in the United States. *Pediatrics,* 114(5):1206–1211.

Stone, P. W. 2009. Economic burden of health associated infections: an American perspective. *Pharmacoeconomics and outcomes research*, 9 (5): 417–422.

Straand, J., Rokstad, K. & Sandvik, H. 1998. Prescribing systemic antibiotics in general practice: a report from More & Romsdal prescription study. *Scandinavian Journal of primary health care,* 16:121-127.

Struelens, M.J. 1998. The epidemiology of antimicrobial resistance in hospital acquired infections: problems and possible solutions. *British medical journal*, 317:652–654.

Struwig, F.W., & Stead B.G. 2001. Planning, designing and reporting research. Cape Town: Pearson Education South Africa.

Suiafan, G.A.R., Shehadeh, M., Darwish, D.A., Al-Ijel, H., Yousef, A. M. & Darwish, R.M. 2012. A cross-sectional study on knowledge, attitude, behaviour related to antibiotic use and resistance among medical and non-medical university students in Jordan. *African journal of pharmacy and pharmacology,* 6(10):763–770.

Survey Monkey https://www.surveymonkey.com

Tansarli, G.S., Athanasiou, S. & Falgas, M.E. 2013. Evaluation of antimicrobial susceptibility of *Enterobacteriaceae* causing urinary tract infections in Africa. *Antimicrobial agents and chemotherapy*, 57(8):3628–3639.

Taylor, D. The literature review: a few tips of conducting it. Health sciences writing center, University of Toronto. http://www.writing.utoronto.ca/advice/specific-types-of-writing/literature-review Date of access: 11 March 2014.

Tenover, F.C. 2006. Mechanisms of antimicrobial resistance in bacteria. *The American journal of medicine*, 19(6A):S3-S10.

Thriemer, K., Katuala,Y., Batoko, B., Alwaronga, J., Devlieger, H., Van Geet, C., Ngbonda, D. & Jacobs, J. 2013. Antibiotic prescribing in DR Congo: a knowledge, attitude and practice survey among medical doctors and students. *Plos One,* 8(2):e55495.

Todar Kenneth. 2012? Todar's Online textbook of bacteriology. http://textbookofbacteriology.net/resantimicrobial.html Date of access: 22 October 2012.

Tiemersma, E.W., Collins, D. & Van den Hof, S. 2014. Summary report: Cost faced by (multidrug resistant) tuberculosis patients during diagnosis and treatment: report from a pilot study in Ethiopia, Indonesia and Kazakhstan. (Submitted to the US Agency for International Development by TB Care I). Management Sciences for Health, Arlington, VA.

Tirunneh, M., Yifru, S., Gizachew, M., Molla, K., Belyhun, Y., Moges, F & Endris, M. 2014. Changing trends in prevalence and antibiotic resistance of uropathogens in patients attending Gondar University Hospital, Northwest Ethiopia. *International journal of bacteriology,* 2014, http://dx.doi.org/10.1155/2014/629424.

Truter, I. 2008. A review of drug utilisation studies and methodologies. *Jordan journal of pharmaceutical sciences,* 1(2):91–104.

Udobi, C.E., Obajuluwa, A.F. & Onaolapo, J.A. 2013. Prevalence and antibiotic resistance pattern of methicillin resistant Staphylococcus aureus from an orthopaedic hospital in Nigeria. *Biomed research international*, 2013/860467:1-4.

University of Toronto. 2008. Literature review: a few tips to writing it. http://www.writing.utoronto.ca/advice/specific-types-of-writing/literature-review Date of access 15 March 2013.

US Department of Health and Human Services. A Comparison of Antibiotic Data. *Agency for healthcare research and quality*. http://www.ahrq.gov/qual/cdifftoolkit/cdiffl2tools2.htm Date of access: 15 September 2012.

Utts, J.M. & Heckard, R.F. 2007. *Mind on statistics*. 3rd ed. Belmont: Brooks/Cole.

Vaccheri, A., Silvani, M.C., Bersaglia, L., Motola, D., Strahinja, P., Vargiu, A., Poluzzi, E. & Montanaro, N. 2008. A 3-year survey of the use of antibacterial agents in five Italian hospitals. *Journal of antimicrobial chemotherapy,* 61:953 – 958.

Van Beneden, C., Lexau., C., Baughman, W., Barnes, B., Bennett, N., Cassidy, M., Pass, M., Gelling, L., Barret, N., Zell, E. & Whitney, C. 2003. Aggregated antibiograms and monitoring of drug-resistant *Streptococcus pneumoniae*. *Emerging infectious diseases,* 9 (9): 1089 – 1095.

Van Bijnen, E. *et al.* 2011. The appropriateness of prescribing antibiotics in the community in Europe: study design. *BMC infectious diseases*, 11:293-297.

Van Boeckel, T.P., Gandra, S., Ashok, A., Caudron, Q., Grenfell, B., Levin, S.A. & Laxminarayan, R. 2014. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. *Lancet infectious disease*, 14: 742 – 750.

Van der Velden, A., duerden, M. G., Bell, J. Oxford, J.S. Altiner, A., Kozlov, R., Sessa, A., Pignatari, A.C. & Essack, Y.E. 2013. Prescriber and patient responsibilities in treatment of acute respiratory tract infections – essential for conservation of antibiotics. *Antibiotics,* 2: 316 – 327.

Van der Walt, C. & Van Rensburg, G. 2011. Fundamentals of research methodology for health care professionals. 2nd ed. Cape Town, Juta & Co.

Vanden Eng, J., Marcus, R., Hadler, J, Imhoff, B., Vugia, D.C., Cieslak, P.R., Zell, E., Deneen, V., McCombs, K., Zansky, S.M., Hawkins, M.A. & Besser, R.E. 2003. Consumer attitudes and use of antibiotics. *Emerging infectious disease*, 9 (9): 1128 – 1135.

Vander Stichele, R.H., Elseviers, M.M, Ferech, M., Blot, S., Goossens, H. & ESAC Project Group. 2004. European surveillance of antimicrobial consumption (ESAC): data collection, performance and methodological approach. *British journal of clinical pharmacology,* 58 (4): 419- 428.

VanGeest, J.B., Johnson, T.B. & Welch, V.L. 2007. Methodologies for improving response rates in surveys of physicians: a systemic review. *Evaluation and the health professions*, 30: 303-321.

Varley, A.J., Sule, J. & Absalom, A.R. 2009. Principles of antibiotic therapy. *Continuing education in anesthesia, critical care and pain*, 9 (6): 84 – 88.

Velasco, E., Espelage, W., Faber, M., Noll, I., Ziegelmann, A., Krause. *et al.* 2011. A national cross-sectional study on socio-behavioural factors that influence physicians' decision to begin antimicrobial therapy. *Infection*; 39: 289-297.

Venmans, L.M.A.J., Hak, E., Gorter, K.J. & Rutten, G.E.H.M. 2009. Incidence and antibiotic prescription rates for common infections in patients with diabetes in primary care over the years 1995 – 2003. *International journal of infectious diseases,* 13: e344 – 351.

Vernaz, N., Huttner, B., Muscionio, D., Salomon, J., Bonnabry, P., Lopez-lozano, J., Beyaert, A., Schrenzel, J. & Harbarth, S. 2011. Modeling the impact of antibiotic use on antibiotic-resistant *Escherichia coli* using population based data from a large hospital and its surrounding community. *Journal of antimicrobial chemotherapy,* 66: 928 – 938.

Vlieghe E, Phoba, M.F., Muyembe, T & Jacobs. J. 2009. Antibiotic resistance among bacterial pathogens in Central Africa: a review of the published literature between 1955 and 2008. *International journal of antimicrobial agents*, 2009, doi:10.1016/j.ijantimicag.2009.04.015.

Verspotten, A., Bolokhovets, G., Ghazarayan, L., Abilova, V., Pyshnik, G., Spasojevic, T. *et al.* 2014. Antibiotic use in Eastern Europe: a cross-national database study in coordination with the WHO Regional Office in Europe. *Lancet infectious diseases, 2014,* http://dx.doi.org/10.1016/S1473-3099 (14)70071-14.

Wattal, C., Joshi., S., Sharma, A., Oberoi., J.K. & Prasad., K..J. 2005. Prescription auditing and antimicrobial resistance at tertiary care hospitals in New Delhi, India. *Journal of hospital infection,* 59: 156 – 158.

Wegner, T. 2007. Applied business statistics: methods and Excel-based applications. 2nd ed. Cape Town, Juta & Co.

Welte,T., Torres, A. & Nathwani, D. 2010. Clinical and economic burden of community-acquired pneumonia among adults in Europe. *Thorax.* (Abstract). http://thorax.bmj.com/content/early/2010/08/19/thx.2009.129502.full.pdf+html Date of access: 3 January 2012.

Wester, C.W., Durairaj, L., Evans, A.T., Schwartz, D.N., Husain, S. & Martinez, E. 2002. Antibiotic resistance. *Archives of internal medicine,* 162:2210–2216.

World Economic Forum. 2013. *Global risks 2013*. Geneva: Author.

World Gastroentorology Organisation. 2012. Acute diarrhea in adults and children: a global perspective. February, 2012.

World Health Assembly. 1998. *Emerging and other communicable diseases: antimicrobial resistance. WHA51.17.* Geneva: Author.

World Health Assembly. 2005. *Improving the containment of antimicrobial resistance*. Geneva: Author.

World Health Assembly. 2007. *Progress report on technical and health matters. WHA A60.28.* Geneva: Author.

World Health Assembly. 2014. Draft global action plan on antimicrobial resistance. Draft for consultation with member states October 2014. Geneva. Author

The World Health Organization. WHONET Software. http://www.who.int/drugresistance/whonetsoftware/en/ Date of access: 5 July 2011.

World Health Organization. 1993. *How to investigate drug use in health facilities*. Geneva: Author.

World Health Organization. 2001. *Global strategy for containment of antimicrobial resistance*. Geneva: Author.

World Health Organization, International working group for drug statistics methodology. 2003a. Introduction to drug utilisation research. Geneva: Author.

World Health Organization. 2003b. Surveillance of antimicrobial resistance. http://who.int/drugresistance/surveillance/en/ Date of access:3 January 2012.

World Health Organization. 2007. Progress in rational use of medicines. *16th World Health Assembly*. Geneva. Author.

World Health Organization. 2009a. Community-based surveillance of antimicrobial use and resistance in resource constrained settings: report on five pilot projects. Geneva: Author.

World Health Organization. 2009b . Country profile of environmental burden of disease – Namibia. Public health and the environment. Geneva: Author. www.who.int/quantifying_ehimpacts/national/countryprofile/namibia.pdf. Date of access: 11 May 2013.

World Health Organization. 2010a. Multidrug and extensively drug resistant TB (M/XDR TB). 2010 Global report on surveillance and response. Geneva: Author.

World Health Organization. 2010b. Namibia country cooperation strategy, 2010-2015.

World Health Organization. 2010c. Medicines: rational use of medicines, fact sheet No 338. http://www.who.int/mediacentre/factsheets/fs338/en/index.html Date of access: 7 October 2012.

World Health Organization. 2011a. The world medicine situation. Geneva: Author.

World Health Organization Collaborating Centre for Drug Statistic Methodology. 2011b. Guidelines for ACT classification and DDD assignment. Geneva: Author.

World Health Organization. 2011c. Antimicrobial resistance fact sheet 194. Geneva: Author.

World Health Organization. 2012a. The evolving threat of antimicrobial resistance – options for action. Geneva: Author.

World Health Organization Collaborating Centre for Drug Statistic Methodology. 2013. Guidelines for ACT classification and DDD assignment 2013. Geneva: Author.

World Health Organization. 2014a. Antimicrobial resistance: global report on surveillance. Geneva: Author.

World Health Organization. 2014b . Antimicrobial resistance: fact sheet no 194 (updated April 2014). http://www.who.int/mediacentre/factsheets/fs194/en/. Date of access: 10 May 2014.

Wood, F., Phillips, C., Brookes-Howell, L., Hood. K., Verheij, T., Coenen, S., Little, P., Melbe, H., Godycki-Cwirko, M., Jakobsen, K., Worby, P., Goossens, H. & Butler, C. 2013. Primary care clinicians' perceptions of antibiotic resistance: a multi-country qualitative interview study. *Journal of antimicrobial chemotherapy,* 68:237–243.

Yah, C.S., Edrin, Y,O. & Odeh, E.N. 2008. Patterns of antibiotic usage by adult populations in the city of Benin, Nigeria. *Scientific research and essay*, 3(3):81-85, March 2008.

Yilgwan, C.S. & Okolo, S.N. 2012. Prevalence of diarrhea disease and risk factors in Jos University Teaching Hospital, Nigeria. *Annals of African medicine*, 11(4):217–221.

You, J.H.S., Yau, B., Choi, K.C., Chau, C.T.S., Haung, Q.R. & Lee, S.S. 2008. Public knowledge, attitudes and behavior of antibiotic use: a telephone survey in Hong Kong. *Infection*, 36:153-157.

Yu, M., Zhao, G., Lundborg, C.S., Zhu, Y., Zgao, Q. & Xu, B. 2014. Knowledge, attitudes and practices of parents in rural China on the use of antibiotics in children: a cross-sectional study. *BMC infectious diseases,* 14:112.

Zarb, P. & Goossens, H. 2011. European Surveillance of Antimicrobial Consumption (ESAC): value of a point-prevalence survey of antimicrobial use across Europe. *Drug*, 71(6):745–755. (Abstract).

Zhang, R., Eggleston, K., Rotimi, V. & Zeckhauses, R. 2006. Antibiotic resistance as a global threat: evidence from China, Kuwait and the United States. *Globalization and health*, 2(6):1-14.

Zhang, l., Li, Y., Zheng, L. & Wang, Z. 2012. Applying “children defined daily dose” to assess appropriate doses in paediatrics. *Journal of evidenced based medicine*, 5 (1):2-15. (Abstract)

Zoutman, D.E., Ford, B.D., Bassili, A.R., Cosby, J.L. & Nakatsu, K. 2008. Factors affecting antibiotic decisions for upper respiratory tract infections I: a survey of family physicians. *International journal of infection control*, 4:1–7.

Annexures

Annexure A – Letter to the laboratory

NORTH-WEST UNIVERSITY
YUNIBESITI YA BOKONE-BOPHIRIMA
NOORDWES-UNIVERSITEIT
POTCHEFSTROOM CAMPUS

Private Bag X6001, Potchefstroom
South Africa 2520

Tel: 018 299-1111/2222
Web: http://www.nwu.ac.za

Medicine Usage in South Africa
Tel: 018 2992288
Fax: 018 2994244
Email: martie.lubbe@nwu.ac.za

Dr. Van Greunen
Pathcare Namibia

27 February 2012

Dear Dr. van Greunen,

The rapid development and spread of antimicrobial resistance is a growing public health concern. The prevalence of resistant micro-organisms in both hospital and community settings is on the increase. However, most resistance and antibiotic utilisation research is carried out in hospital settings, and well-documented information about community use and resistance patterns is limited. The rise in antimicrobial resistance has the potential to increase direct healthcare resources and costs for treating patients.

In 2001, WHO developed a global strategy for Containment of Antimicrobial Resistance, of which one strategy is the establishment of effective surveillance of antimicrobial use and resistance among common pathogens in the community and hospital settings?

My name is Dineo Dawn Pereko, a pharmacist currently pursuing a PhD in Pharmacy Practice at the North-West University. For my thesis, I will be working on determining the prescribing patterns (including factors influencing prescribing), appropriateness, prevalence and cost implications of antibiotic usage in the Namibia private sector and comparing with antibiotic sensitivity data. The study is expected to provide valuable and unique data concerning resistance patterns and prescription behaviour in Namibia private sector. It will provide recommendations on improving antibiotic use and thus contribute to controlling resistance development.

Part of my data collection will include analyzing claims data to determine use (expressed as DDD/population unit), reviewing patient prescriptions and conducting a survey to determine knowledge attitudes and practice in antibiotic prescribing. To make the study complete, I would like to work with PathCare especially in accessing sensitivity data from your database.

The results of the study will be shared with professional associations in Namibia so that collectively we can improve antimicrobial stewardship. The study is fully supported by the research entity, Medicine Usage in South Africa (MUSA) at the North-West University.

Yours sincerely

Mrs Dawn Pereko

Prof Martie S Lubbe
Leader: Medicine usage in South Africa
School of Pharmacy
North-West University
Potchefstroom Campus
Potchefstroom
2520

Original details: Engela Oosthuizene(12639532) C:\Users\NWUuser\Desktop\MUSA\Studente databasis\Dineo Pereko\Letter 1.docm
27 February 2012

File reference: 7.1 Studente Administrasie

Annexure B – Letter to Professional Associations

NORTH-WEST UNIVERSITY
YUNIBESITI YA BOKONE-BOPHIRIMA
NOORDWES-UNIVERSITEIT
POTCHEFSTROOM CAMPUS

Private Bag X6001, Potchefstroom
South Africa 2520

Tel: 018 299-1111/2222
Web: http://www.nwu.ac.za

Medicine Usage in South Africa
Tel: 018 2992288
Fax: 018 2994244
Email: martie.lubbe@nwu.ac.za

10 March 2014

Dear colleagues,

The rapid development and spread of antimicrobial resistance is a growing public health concern. The prevalence of resistant micro-organisms in both hospital and community settings is on the increase. However, most resistance and antibiotic utilisation research is carried out in hospital settings, and well-documented information about community use and resistance patterns is limited.

In 2001, WHO developed a global strategy for Containment of Antimicrobial Resistance, of which one strategy is the establishment of effective surveillance of antimicrobial use and resistance among common pathogens in community and hospital settings.

Working with the medical insurance and PathCare, a PhD student in Pharmacy Practice at North-West University Dineo Dawn Pereko is working on a study to assess both antibiotic use and resistance in Namibia. The objective of the study is to review and analyze antibiotic use data in Namibia and compare with antibiotic susceptibility data; to understand patient knowledge and attitudes as well as prescriber practices with respect to antibiotics. The study is expected to provide valuable and unique data concerning resistance patterns and antibiotic prescribing practice in Namibia private sector. It will provide recommendations on improving antibiotic use and thus contribute to controlling resistance development.

Your assistance is required in collecting data for this study by completing a short on-line survey on antibiotic prescribing practices.

The survey is anonymous and voluntary. The study is fully supported by the research entity, Medicine Usage in South Africa (MUSA) at the North-West University.

Yours sincerely

Mrs Dawn Pereko

Prof Martie S Lubbe
Leader: Medicine usage in South Africa
School of Pharmacy
North-West University
Potchefstroom Campus
Potchefstroom
2520

Annexure C – Patient Informed Consent

NORTH-WEST UNIVERSITY
YUNIBESITI YA BOKONE-BOPHIRIMA
NOORDWES-UNIVERSITEIT

Participant Information Leaflet

Our research team is describing the knowledge of antibiotics among the public who receive their treatment in the private health sectors in Windhoek. We are specifically looking to understand how much the public knows about antibiotics and how they use them.

For us to be able to do this, we need your permission to fill out a questionnaire. The questionnaire is anonymous; therefore there is no need for you to give your name. The questionnaire will be completed by you either at the pharmacy or the doctor's consulting room.

Your information will help determine how best antibiotics can be used by the public. Your participation is completely voluntary, i.e., you don't have to participate in this study if you don't want to. Your health care and medical/drug treatment will not be affected if you choose not to participate.

You can withdraw from the study at any time, again with no impact on your health care and medical/drug treatment at the hospital/clinic. If you kindly agree to participate, we need you to sign this consent form and complete the attached questionnaire.

You may call the researchers at any time for further information as follows:

Dineo Pereko
061 307711
tkpharmacy@iway.na

We thank you for your time and your assistance.

NORTH-WEST UNIVERSITY
YUNIBESITI YA BOKONE-BOPHIRIMA
NOORDWES-UNIVERSITEIT

Consent Form

I _____, hereby confirm that I have received a participant information leaflet, have understood the nature of the study and am willing to participate in the study. I understand that participation is voluntary and that I can withdraw from the study at any time without affecting my health care and medical/drug treatment.

_____
Signature

Signed this _____ day of _____ 2012 at _____

Witness 1: _____

Witness 2: _____

Annexure D – Public/Patient Survey Questionnaire

NORTH-WEST UNIVERSITY
YUNIBESITI YA BOKONE-BOPHIRIMA
NOORDWES-UNIVERSITEIT
POTCHEFSTROOMKAMPUS

Private Bag X6001, Potchefstroom
South Africa, 2520

Medicine Usage in South Africa
Faculty of Health Sciences
Tel: (018) 2992288
Fax: (018) 2994244

SURVEY ON THE KNOWLEDGE OF ANTIBIOTICS USE AMONG AMBULATORY PATIENTS IN THE PRIVATE SECTOR OF NAMIBIA

INTRODUCTION:

The rapid development and spread of resistance of bacteria to antibiotics is a growing public health concern. This study aims to determine how much the general population knows about antibiotics and how they use these medicines. The findings of the study will help develop measures that can educate patients and improve use of antibiotics in Namibia and thus spare these important medicines.

Participation required from you is only to complete this form. You are under **no** obligation to participate in this study. If you agree to participate in the study, please note that this survey is anonymous and your responses cannot be traced back to you. As far as possible, please be brief and specific in your responses.

I. GENERAL INFORMATION:

1. Gender: Male ☐ Female: ☐

2. Age _____ DoB: _____

3. Medical Aid Yes ☐ No ☐

4. Employed Yes ☐ No ☐

5. Education level - what level of education have you completed?

   Grade 7 and under ☐
   Grade 8 - 10 ☐
   Grade 11-12 ☐
   Tertiary education ☐

II. KNOWLEDGE OF ANTIBIOTICS:

6. Have you used antibiotics in the past year? Yes ☐ No ☐

7. How did you get the antibiotic? (Mark more than one, if necessary)

Prescribed by doctor	Yes ☐	No ☐
Bought from pharmacy (no prescription)	Yes ☐	No ☐
Got from friend	Yes ☐	No ☐
Had some left over at home	Yes ☐	No ☐

8. What were your symptoms that made you use the antibiotic?? List all.

_____

_____

_____

9. If you saw the doctor, what did the doctor say was wrong with you (diagnosis)?

_____

10. Did you request for an antibiotic from the doctor? Yes☐ No☐

11. Were you given instructions on how to use the antibiotic? Yes☐ No☐

12. When did you stop taking your antibiotics?
when you felt better ☐
when the antibiotic was finished☐

13. Where do you get your information on antibiotics from? Name 3 sources if applicable

a. _____

b. _____

c. _____

14. For the following statements, answer true or false

Statement	True	False
a. Antibiotics kill viruses		
b. When I have a cold, I should take antibiotics to get better quicker		
c. When I have a cold, I should take antibiotics to prevent getting worse		
d. When I visit a doctor sick enough with cold, I usually expect an antibiotic		
e. Unnecessary use of antibiotics makes them ineffective		

YOU HAVE JUST FINISHED THE SURVEY……THANK YOU VERY MUCH.
We are very appreciative of your time in completing this survey.

NORTH-WEST UNIVERSITY
YUNIBESITI YA BOKONE-BOPHIRIMA
NOORDWES-UNIVERSITEIT
POTCHEFSTROOMKAMPUS

Private Bag X6001, Potchefstroom
South Africa, 2520

Medicine Usage in South Africa
Faculty of Health Sciences
Tel: (018) 2992288
Fax: (018) 2994244

OPNAME OOR DIE KENNIS VAN ANTIBIOTIKA-GEBRUIK ONDER AMBULANTE PASIËNTE IN DIE PRIVAATSEKTOR VAN NAMIBIË

INLEIDING:

Die snelle ontwikkeling en verspreiding van weerstand van bakterieë teen antibiotika is 'n groeiende bekommernis in openbare gesondheidsorg. Hierdie studie het ten doel om te bepaal hoeveel die algemene bevolking van antibiotika weet en hoe hulle hierdie medisyne gebruik. Die bevindinge van die studie sal help om maatreëls te ontwikkel wat pasiënte kan opvoed en om die gebruik van antibiotika in Namibië te verbeter en dus hierdie belangrike medisyne te spaar.

Deelname wat van jou verlang word, is om slegs hierdie vorm te voltooi. Jy is onder **geen** verpligting om aan hierdie studie deel te neem nie. As jy instem om aan die studie deel te neem, let asseblief daarop dat hierdie opname anoniem is en jou antwoorde kan nie na jou teruggespoor word nie. Hou asseblief jou antwoorde so ver moontlik kort en spesifiek.

I. ALGEMENE INLIGTING:

1. Geslag: Manlik ☐ Vroulik: ☐

2. Ouderdom _____ Geb. Datum: _____

3. Mediese Fonds Ja ☐ Nee ☐

4. Werk Ja ☐ Nee ☐

5. Vlak van opleiding – watter vlak van opleiding het jy voltooi?

Graad 7 en laer	☐
Graad 8 – 10	☐
Graad 11-12	☐
Tersiêre opleiding ☐	

II. KENNIS VAN ANTIBIOTIKA:

6. Het jy in die afgelope jaar antibiotika gebruik? Ja☐ Nee ☐

7. Hoe het jy die antibiotikum gekry? (Merk meer as een indien nodig)

Voorgeskryf deur dokter	Ja☐	Nee☐
Gekoop by apteek (geen voorskrif)	Ja☐	Nee☐
By vriend gekry	Ja☐	Nee☐

Het nog by die huis oorgehad Ja☐ Nee☐

8. Wat was die simptome wat jou die antibiotikum laat gebruik het? Lys almal.

_____

_____

_____

9. Indien jy 'n dokter gespreek het, wat het die dokter gesê is verkeerd met jou (diagnose)?

_____

10. Het jy die dokter vir 'n antibiotikum gevra? Ja☐ Nee☐

11. Is jy aanwysings gegee van hoe om die antibiotikum te gebruik? Ja☐ Nee☐

12. Wanneer het jy opgehou om jou antibiotika te gebruik?
toe jy beter gevoel het ☐
toe die antibiotikum klaar was ☐

13. Waar kry jy inligting oor antibiotika? Noem 3 bronne indien van toepassing.

a. _____

b. _____

c. _____

13. Dui aan of the volgende stellings waar of vals is

Stelling	Waar	Vals
a. Antibiotika dood virusse		
b. As ek verkoue het, moet ek antibiotika gebruik om gouer gesond te word		
c. As ek verkoue het, moet ek antibiotika gebruik om te keer dat dit erger word		
d. As ek siek genoeg aan verkoue is en 'n dokter spreek, verwag ek gewoonlik 'n antibiotikum		
e. Onnodige gebruik van antibiotika maak hulle oneffektief		

JY HET PAS DIE OPNAME VOLTOOI……BAIE DANKIE.
Ons het hoë waardering vir die tyd wat jy afgestaan het om hierdie opname te voltooi.

Annexure E – Prescriber Survey Questionnaire

NORTH-WEST UNIVERSITY
YUNIBESITI YA BOKONE-BOPHIRIMA
NOORDWES-UNIVERSITEIT
POTCHEFSTROOMKAMPUS

Private Bag X6001, Potchefstroom
South Africa, 2520

Medicine Usage in South Africa
Faculty of Health Sciences
Tel: (018) 2992288
Fax: (018) 2994244

SURVEY ON THE KNOWLEDGE AND PRESCRIPTION PRACTICES OF ANTIBIOTICS USE IN THE PRIVATE SECTOR OF NAMIBIA

INTRODUCTION:

The rapid development and spread of antimicrobial resistance is a growing public health concern. The prevalence of resistant micro-organisms in both hospital and community settings is on the increase. However, most resistance and antibiotic utilization research is carried out in hospital settings, and well-documented information about community use and resistance patterns is limited.

The objective of the study is to review and analyze antibiotic use data in the private health sector of Namibia and compare with antibiotic susceptibility data. The study is expected to provide valuable and unique data concerning resistance patterns and prescription practice in the Namibia private health care sector. It will provide recommendations on improving antibiotic use and thus contribute to controlling resistance development.

Your assistance is required in collecting data for this study. However you are under no obligation to participate in the study. If you do decide to participate in the study, please note that this survey is anonymous. As far as possible, please be brief and specific in your responses

I. GENERAL INFORMATION:

1. Gender: Male ☐ Female: ☐
2. Age group (years): 26 to ≤ 35☐ >36 to ≤ 45☐ >46 to ≤-55☐ >55☐
3. Provider type: GP ☐ Specialist ☐ _____(specialty)
4. In which sector do you practice predominantly? Public ☐ Private☐ Both ☐
5. For how long have you been practicing as a medical doctor? _____ year(s)
6. In which region do you practice? _____
7. On average (roughly) how many patients do you see a day?

Under 25 ☐
26 – 50 ☐
51 – 75 ☐
More than 75 ☐

8. Do you belong to a professional association? Yes ☐ _ (please state which below)

_____

No ☐

9. Do you have a copy of the Namibia Standard Treatment Guidelines? Yes ☐ No ☐

II. USE OF ANTIBIOTICS:

10. Do you think there is a problem with antibiotic use in Namibia? Yes ☐ No ☐

11. How would you classify the antibiotic use problem in Namibia (select all that apply)
Over prescribing ☐ under prescribing ☐ inappropriate use by patients ☐

Other _____

12. Are you aware of the bi-annual resistance data available for Namibia?

☐ Yes No ☐

If yes, how do you receive these data?

_____

13. For the following question, please provide the required information on the table below. For antimicrobial treatment, what do you usually use as first line? Where applicable, please provide additional comments

Infection	Do Routine Laboratory Culture		Laboratory Culture when Empirical Treatment Fails		Antibiotic / Antimicrobial Treatment
	Yes	No	Yes	No	
Acute pharyngitis					
Nasopharyngitis					
Acute otitis media					
Chronic otitis media					
Acute sinusitis					
Bronchitis					
Pneumonia					
Cystitis					
Pyelonephritis					

III. IN REFERENCE TO YOUR REGULAR PRACTICE:

The following questions are related to your antibiotic use and prescribing patterns in your regular practice and work area.

14. When following up a patient, do you evaluate antibiotic treatment adherence? Adherence is defined as a patient strictly following medical indications with regard to dosage administration and frequency.

    Yes ☐ always ☐ sometimes ☐

    No ☐

15. Do you have written materials for your patients that talk about dosage, adherence and compliance with the antibiotic regimen?

    Yes ☐ No ☐

16. What are your main sources of information on antibiotics? (please rank from 1 to 4 according with priorities) [For example, 1=first priority, or most frequent sources, etc.]

    a. ☐ scientific journals
    b. ☐ scientific events
    c. ☐ professional associations
    d. ☐ pharmaceutical industry (medical reps)

17. What do you think would improve prudent use of antibiotics in Namibia? List 3 thoughts.

18. Do you think there should be CPD sessions on antibiotics? Yes ☐ No ☐

    Indicate a training need _____

YOU HAVE JUST FINISHED THE SURVEY.....THANK YOU VERY MUCH

We are very appreciative of your time in completing this survey. It is our hope that analysis of results will be instrumental improving rational use of antibiotics in Namibia.

Annexure F - Author Guidelines

Manuscript 1- Journal of Infection in Developing Countries Guidelines

Author Guidelines

Overview of the publication and peer review processes

JIDC aims to provide all authors with an efficient and consistent editorial process. Submitted manuscripts will be assigned to a member of the editorial team who is an expert in the field. The editor will assess the manuscript to determine whether it is within the scope of the journal, the quality of the data presented, and the standard of presentation before sending it for peer review.

Authors are required to provide the contact details (including email addresses) and area of expertise of three potential peer reviewers. These suggested reviewers should be experts in the field of study relevant to the manuscript and should not be members of the same research or academic institution as the authors. Author-suggested reviewers will be considered alongside other potential reviewers identified by their publication record or recommended by Editorial Board members. However, the final decision on the choice of reviewers rests with the editor without any obligation to contact any of the author-recommended peer reviewers.

Manuscripts will be sent to two reviewers who will be asked to assess whether the manuscript is technically and scientifically sound and coherent and the quality of the writing is acceptable. The final editorial decision is made based on the recommendations of the peer reviewers, provided these recommendations are in accord without any strong dissenting opinions. Where there are dissenting or opposing views, the paper is assessed by a third reviewer who may or may not be a member of the journal's Editorial Board. Once all reviews have been received and considered by the editors, a final decision is made and a letter drafted to the corresponding author. Possible final decisions include:

- Acceptance without revision
- Acceptance subject to minor revision
- Resubmission for review after major revision
- Declined

Where there are issues with the standard of presentation or clarity of language, the authors will be informed accordingly and provided with suggestions or assistance for rectification

Editorial policies

Any manuscript submitted to the journal must not be under consideration by any other journal or already published in any journal or other citable form. Submission of a manuscript to JIDC implies that all authors have read and agreed to its content and take responsibility for the reported findings. Authors are expected to state that the study (where applicable) has been conducted with approval of an appropriate ethics committee. Additionally, all research carried out on humans must be in compliance with the Helsinki Declaration, and animal studies must follow internationally recognized guidelines. The authors are expected to include a statement to this effect in the Methodology section of the manuscript. The name of the ethics approval body should also be provided. Informed consent for participation in the study and the use of clinical photographs of individual patients must also be documented. Manuscripts submitted by authors from pharmaceutical companies or commercial organizations

that sponsor clinical trials, as well as those from individuals and companies working on industry-sponsored research, should adhere to the Good Publication Practice guidelines for pharmaceutical companies. These guidelines are designed to uphold responsible and ethical standards in the reporting of industry-sponsored clinical trials and research.

JIDC supports initiatives to improve the performance and reporting of clinical trials. This objective includes the prospective registration and numbering of clinical trials of health-care interventions (See International Committee of Medical Journal Editors {ICMJE}-http://www.icmje.org/clin_trialup.htm). Protocols or reports of controlled trials of health-care interventions should be registered in a suitable publicly accessible registry before submission in JIDC. The trial registration number should be provided at the time of article submission. A list of trial registers that meet the ICMJE guidelines are available athttp://www.icmje.org/faq.pdf.

JIDC also supports current initiatives for improving the reporting of biomedical research. Checklists have been developed for randomized controlled trials (CONSORT), systematic reviews (QUORUM), meta-analyses of observational studies (MOOSE), diagnostic accuracy studies (STARD), assessing the quality of evidence (GRADE) and qualitative studies (RATS). Authors should utilize the appropriate checklist during the preparation of their manuscripts. JIDC peer reviewers will be asked to refer to these checklists when evaluating the manuscript.

The involvement of medical writers or anyone else who assisted with the preparation of the manuscript content as well as any source(s) of funding should be mentioned in the Acknowledgement section. Any "in press" articles cited within the references and necessary for the reviewers' assessment of the manuscript should be made available if requested by the editorial office. Authors of accepted papers will be requested to provide a declaration of competing interests which will be included in the Acknowledgements section of the paper.

Submission Process

Submissions from around the world are encouraged but all manuscripts must be submitted in English. At submission, authors will be requested to assign their manuscripts to one of the available sections.

The corresponding author must set up a JIDC account to submit their manuscript. All authors are requested to subscribe to the newsletter and become a JIDC member. This will ensure that all authors get up-to-date information from JIDC including when their manuscript is first published.

Please note that by signing up/submitting your manuscript to JIDC you agree to terms and conditions; if you would not like to be contacted by JIDC or affiliating companies please inform us.

Cover Letter

All manuscripts submitted to JIDC, must be accompanied by a letter declaring that the manuscript has not been submitted or accepted for publication elsewhere. Authors should suggest three potential unbiased reviewers (with email addresses) who are qualified to review their manuscript. This letter must warrant that all authors have seen and approved the content and have contributed significantly to the work. A cover letter must also accompany a revised submission and must address, point by point, issues raised in the review process.

Organization of the Manuscript

Articles should be typed double spaced using twelve point Times New Roman or other serif font.

Original Articles: These should be organized in the following sections: Title page, Structured Abstract (see below), Introduction, Methodology, Results, Discussion, Conclusion, Acknowledgments, References (not to exceed 50), Figures, Figure Legends, Tables & captions, Authors' contributions.

Brief original articles: The text for Brief Articles should not exceed a total of 2100 words, including an abstract (not to exceed 250 words), references (not to exceed 30), figures (not more than 3), and tables (not to exceed 3). Subdivisions of sections are encouraged to help orient the reader.

Case reports: These should describe case diagnosis and investigations or treatments which are of exceptional interest, highlighting novel and important findings. Please refer to the short communications section for length and other specifications.

Letters to the editor: The text for letters the editor should not exceed a total 1,200 words. References (not to exceed 15), figures (not more than 2) and tables (not to exceed 2). Subdivisions of sections are encouraged to help orient the reader but should be general, such as "The Study" and "Conclusions". Letters to the editor are generally updates on recent infectious disease trends and research, but may also respond to recent articles published in JIDC.

Reviews: These are summaries of developments in areas related to infection in developing countries which are of broad interest to the target audience of the journal. These are usually invited, but authors identifying a need and wishing to submit a review article are welcome to contact the Editorial Office. Authors are advised to contact the Editorial Office before commencement of writing to ensure that a similar topic has not already been commissioned to another reviewer.

Layout of Manuscripts

Title Page

The title page should include the title of the manuscript as well as the full names and institutional affiliations for all authors. The corresponding author should also be indicated.

Title: The title should contain no more than **125 characters** (including spaces) and should be specific to the study. It should be comprehensible to a broad spectrum of readers.

Authors and Affiliations: This section should include the first names, middle initials (if used), surnames, and affiliations (university or organization), department, city, state/province (if applicable), and country for all authors. The institution/laboratory where the work was conducted should be indicated. One of the authors should be designated as the corresponding author. Full contact details including postal address, telephone and fax numbers, and email address for the corresponding author must be provided. Where the article is being submitted on behalf of a consortium, a listing of all consortium members and affiliations should be included after the Acknowledgements.

Running title: A running title of not more than **50 characters** (including spaces) must be provided

Key words: The authors must provide **3 to 6 keywords**.

Abstract

A **structured** abstract **not exceeding 250 words** must be provided. It should be divided into the following sections: Introduction, Methodology, Results, and Conclusions. Citations, tables and specialist abbreviations should be avoided. The techniques used must be mentioned without going into methodological detail and the most important findings should be summarized.

Introduction

The introduction should put the focus of the manuscript into a broader context and be written in a way

understandable to researchers without specialist/expert knowledge in the area. Relevant controversies or disagreements in the field should be mentioned. The key aspects of the literature should be reviewed with the aim of indicating why the study was necessary and what it would contribute to the field of study. The introduction should conclude with a comment about the overall aims of the study.

Methodology

This section should include the design of the study, the setting, the type of participants or materials involved, as well as a description of all interventions and comparisons. The authors should also provide a description of the type of statistical analysis used, including a power calculation when appropriate. Well-established methodologies should simply be mentioned and referenced appropriately. For new methods, the protocols for the method should be included. The authors should provide enough detail to enable reproduction of the findings. JIDC encourages the submission in the form of separate supporting information files, all appendices, detailed protocols, or details of the algorithms pertaining to new protocols or less well-established methods. These are published as online appendices but they are linked to the main article in a fully searchable format. Generic drug names should generally be used and in cases where proprietary brands have been used, the brand names must be included in parenthesis. Where available, the accession numbers of any nucleic acid sequences and protein sequences cited in the manuscript and the corresponding database name should be provided. When referencing a manufacturer with reagents or equipment used, the city and country where the manufacturer is located should also be provided.

Results

The results section should be written in past tense and should provide details of findings that are required to support the conclusions made in the manuscript. To enhance clarity, the section may be divided into subsections, each with a concise subheading. Where appropriate, results of statistical analysis should include analysis of relative/absolute risks and confidence analysis. Large datasets, including raw data, may be submitted as supporting files for publication as supplementary appendices.

Discussion

The discussion should clearly identify the main conclusions of the study. Authors should provide a clear explanation of the importance and relevance of these conclusions. Speculations on how the conclusions fit in or affect the existing assumptions or models should be explored. Suggestions for further key experiments for future work can be included. Summary illustrations may be included. When appropriate, issues related to resource limitations faced by the researchers during the course of the study, how these were addressed, and suggestions for improvement may also be included.

Acknowledgments

Those who have made substantial contribution to the study in terms of design, execution, analysis or manuscript drafting/revision but do not fit the criteria for authorship should be mentioned in this section. It is the responsibility of the authors to ensure that those being acknowledged have agreed to being named in such capacity. The source of funding for the study should be stated in this section.

References

Published communication

Only published articles or accepted manuscripts (in press) should be included in the list of references. All other published reports such as government reports, WHO reports and documents, books and manuals should be cited

using the numbered citation method described below. Simple website addresses (*e.g.*, an online biological resource such as *Entrez*) should be included in the text.

Unpublished communication

Conference abstracts or articles which have been submitted but not yet accepted for publication and personal communications should not be cited in the reference list.

Personal communications include letters, memos, personal interviews, telephone conversations, emails, messages from discussion lists and electronic bulletin boards. Citations for this type of material are not included in the reference list because they do not contain recoverable data. Cite personal communications in the text only. Adding "personal communication" to the citation within the text is a useful indicator of the kind of information under discussion. Give the initials as well as the surname of the communicator and provide as exact a date as possible.

M. Jones (personal communication, August 03, 2012) finds the project meets several criteria ...

Professor Ahmod in an email to the author gave details of her clinical experience with this treatment (N. M. Ahmod, personal communication, January 12, 2013).

Format

JIDC uses the numbered citation method. The references must be listed and numbered consecutively in the order in which they appear in the text followed by those appearing in figures and tables. Citations should be indicated by their unique reference number in square brackets in the text. Where there are multiple citations within a single set of brackets these should be separated by commas with no spaces between the comma and the next number. If there are three or more sequential citations, the numbers should be given as a range. Example: "……previously described above [1,6-8,26]."

Authors are encouraged to keep the number of references limited to those that are important for the understanding of the manuscript.

JIDC recommends the use of referencing software such as Zotero, which is Free for download at www.zotero.org

If you have any problems using any of this software, please contact the respective company for technical advice.

Reference format examples:

Published Papers

1. Raghu MB, Deshpande A, Chintu C (1981) Oral rehydration for diarrhoeal diseases in children. Trans R Soc Trop Med Hyg 75: 552-555.

In Press Papers

2. Kharitonov SA, Barnes PJ Clinical aspects of exhaled nitric oxide. Adv Clin Path. In press.

Article within a journal supplement

3. Baquero F, Barrett JF, Courvalin P, Morrissey I, Piddock L, Novick WJ (1999) Epidemiology and mechanisms of resistance among respiratory tract pathogens. Clin Microbiol Infect 4 Suppl 2: 19-26.

Electronic Journal Articles

4. Loker WM (1996) "Campesinos" and the crisis of modernization in Latin America. Jour Pol Ecol 3. Available:http://www.library.arizona.edu/ej/jpe/volume_3/ascii-lokeriso.txt. Accessed 11 August 2006.

Books

Whole Book

5. Lucas AO and Gilles HM (2003) Short textbook of public health medicine for the tropics, 4th edition. London: Arnold Press 389 p.

Book Chapters

6. Fernández E and Torres AC (2006) Gender differentials in health. In Jamison DT, Bremen JG, Measham AR, Alleyne G, Cleason M, Evans DB, Jha P, Mills A, Musgrove P, editors. Disease Control Priorities in Developing Countries. New York: Oxford University Press. 195-210.

Accession Numbers

We encourage authors to deposit relevant datasets, images, nucleotide and protein sequences and microarray data in public resources. The relevant accession numbers and where appropriate the version numbers of such deposited material should be mentioned. Suggested databases include, but are not limited to

-Microarray data: ArrayExpress ; Gene Expression Omnibus [GEO]

-Nucleotide sequences: DNA Data Bank of Japan [DDBJ] ; European Molecular Biology Laboratory (EMBL/EBI) - Nucleotide Sequence Database, or GenBank (National Center for Biotechnology Information).

-Protein sequences: UniProtKB/Swiss-Prot; Protein Data Bank

-Computional modeling: BioModels Database

-Plasmids: Addgene, or PlasmID,Database of Interacting Proteins

-Chemical structures and assays: PubChem Substance; PubChem BioAssay

"-Multilocus sequence typing data for bacteria: www.mlst.net

Requirements:

Abbreviations

Abbreviations must be defined when they are first used in the text.

Nomenclature & Taxonomy

JIDC recommends the use of correct and established nomenclature wherever possible:

- SI units should be used throughout
- Genus and Species names should be italicized (*e.g.*, *Plasmodium falciparum*). Where the genus appears in the title it should be written out in full. In the main text, the genus should be written out in full at first mention and thereafter abbreviated*e.g.* (*P. falciparum*). Authors must ensure that there is no confusion with other genera mentioned in the text. The spelling and taxonomy of names of microorganisms should follow internationally accepted nomenclature.
- Genes, mutations, genotypes, and alleles should be italicized. Authors should consult appropriate genetic nomenclature databases (*e.g.*, HUGO) for human genes for the recommended names. Proteins are not normally italicized.
- The Recommended International Non-Proprietary Name (rINN) of drugs should be provided. Commercial names of other products should only be used where there is no other suitable term for the product. In such cases, the name, city and country of the manufacturer should be provided in parenthesis at the first mention of the product.

Figures & Tables

Figures and tables should not be integrated into the main text. They must be submitted as separate supplementary files and never be included in the same manuscript text. Figures should appear on separate files

with all tables saved in one document. They should be numbered consecutively using Arabic numerals (Figure1, Figure 2, Figure 3, Table 1, Table 2, Table 3, *etc.*). Results which can be described as short statements within the text should not be presented as figures or tables. Footnotes should be used to explain abbreviations. Citations should be indicated using the style outlined under "References" above. Large tables can be provided as supporting information for publication along with the article.

Important: For MEDLINE/PubMed compliance, all images MUST be at or above the intended display size, with the following image resolutions: Line Art 800 dpi, Combination (Line Art + Halftone) 600 dpi, Halftone 300 dpi. Low resolution (72dpi, web-like res) are NOT acceptable. Check this table for immediate reference.

Figure Legends and Captions for Tables

Captions for tables and legends for figures should be typed double spaced in the main text and appear on a separate page. Captions for figures should NOT appear in the figures; however, when uploading the figures to the website, please ensure that the files are appropriately identified as Figure 1, Figure 2, etc.. The legends and captions should help make the figures and tables understandable without the reader having to refer to the main text. However, they should be concise and should not be used to re-describe the methodology.

Multimedia and Other Supporting Files

Authors are welcome to submit supporting files and multimedia files along with their manuscripts. These materials will also be subject to peer review. Supporting files can be in the form of Dataset, Figure, Table, Text, Protocol, Audio, or Video. These should be referred to in the text as supporting (*e.g.* Table 4-S) refers to the fourth supporting information table. Titles of all supporting material should be listed at the end of the manuscript under the heading "Supporting Information."

Cover Letter

All submitted manuscripts should be accompanied by a cover letter which explains why the manuscript is suitable for publication in JIDC.

Submission of Manuscripts

Submission to the JIDC is free and open to everyone. You have to **register** on this site, and **enroll as Author**, before you can be author of a submission.

Prior to starting the submission, authors are required to carefully read the following guide, which contains detailed instructions on how to properly format your files and data:

http://www.jidc.org/index.php/journal/pages/view/submission

Manuscripts and all the necessary additional files are submitted on the site, using the new submission wizard at:

http://www.jidc.org/index.php/journal/author/submit

***IMPORTANT: Please note that the JIDC cannot be held responsible for emails from the editors or proofreaders that are not received by authors due to errors in spam filters on public email servers such as Yahoo, Hotmail or Gmail, or your company / insitutional policies.
Please add jidc.org to your email service's trusted email list and/or make sure to frequently check online for changes in your manuscript's status.

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. The submission has not been previously published, nor is it before another journal for consideration (or an explanation has been provided in Comments to the Editor).

2. The text adheres to the stylistic and bibliographic requirements outlined in the Author Guidelines, which is found in About the Journal.
3. You have printed and carefully read the Submission Walkthrough guide, and applied all the requirements included therein.
4. The manuscript text file does not include any image or table.
5. Tables are all placed in a single file, one per page, with appropriate placeholders within the text.
6. All the images are placed in separate files, in TIFF or EPS file format, and adhere to the PMC reference table. **Images included in Microsoft OfficeWord file formats WILL NOT be accepted.**

Copyright Notice

Authors who publish with this journal agree to the following terms:

a. Authors retain copyright and grant the journal right of first publication with the work simultaneously licensed under aCreative Commons Attribution License that allows others to share the work with an acknowledgement of the work's authorship and initial publication in this journal.

b. Authors are able to enter into separate, additional contractual arrangements for the non-exclusive distributio of the journal's published version of the work (e.g., post it to an institutional repository or publish it in a book) with an acknowledgement of its initial publication in this journal.

c. Authors are permitted and encouraged to post their work online (e.g., in institutional repositories or on their website) prior to and during the submission process, as it can lead to productive exchanges, as well as earlier and greater citation of published work (See The Effect of Open Access).

Privacy Statement

The names and email addresses entered in this journal site will be used exclusively for the stated purposes of this journal and will not be made available for any other purpose or to any other party.

Author Fees

This journal charges the following author fees.
Article Publication: 244.00 (EUR)
If this paper is accepted for publication, you will be asked to pay an Article Publication Fee to cover publications costs. Total amount includes VAT.

>> IMPORTANT: Since the JIDC does not provide paid fast track review service, you are kindly requested not to make your payment before the submission is accepted for publication.

If you can't use PayPal to pay the fee, please contact billing@jidc.org for detailed instructions.

If you do not have funds to pay for Submission fees, please send immediately a written request signed by your Institution to the following mail address: waiverequest@jidc.org. Specific reasons for submission fees waiver

should be indicated in this letter which will be submitted to the Editorial Board. Requests sent during the article editing process will not be accepted.

Manuscript **2 – Iranian Journal of Public Health Author Guidelines**

http://ijph.tums.ac.ir/index.php/ijph/about/submissions#authorGuidelines accessed on 06 June 2015.

Iranian Journal of Public Health Author Guidelines

Manuscript 2

Author Guidelines

The "**Iranian Journal of Public Health (IJPH)** "is the official scientific quarterly publication of the **School of Public Health & Iranian Public Health Association.**

It accepts Original Papers, Review Articles, Short Communications, Case Reports and Letters to the Editor in the fields of Public Health. All correspondences should be addressed to:

The Editor-in-Chief, Iranian J Publ Health

P.O. Box: 14155-6446. Tehran, Iran

Tel/Fax: + 98-21-88950184

E-mail: ijph@tums.ac.ir

URL: http://ijph.tums.ac.ir

Submitted manuscript, should embrace the following criteria:

- Content should not be related to local issues but preferably with critical national or global items.
- Having innovative and creative outcome.
- Methods should preferably be advanced and reproducible.
- IJPH accepts manuscripts written in American English.

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. **Types of Manuscripts**

Original articles:

These include randomized controlled trials, intervention studies, studies of screening and diagnostic test, outcome studies, and cost effectiveness analyses. The text of original articles amounting to utmost 3000 words (excluding Abstract, References and Tables) should include: **Title**; the **Abstract**; **Introduction**; **Materials & Methods**; **Results**; **Discussion**; **Conclusion; Acknowledgement; References, Tables and Figures**.

Review Articles:

They should be written by authors considered experts on the subject. Therefore the corresponding author of the review article must be one of the authors of at least three articles presented in Reference section. Systematic reviews and meta-analysis are more welcomed and they should respectively follow the PRISMA (http://www.prisma-statement.org/) and MOOSE guidelines (http://www.consort-statement.org). Review articles must include an abstract of no more than 250 words, a main text between 2000-3000 words excluding up to 90 references, and up to 6 tables and/or figures.

Short Communications:

Short communications are brief reports of research works containing new findings, which are not exceeding 2500 words from introduction through references. The Short Communication consists of Abstract, main body including Introduction, Methods, Results, Discussion, Conclusion; Acknowledgement, References, Tables and Figures.

Case reports:

Case reports are accepted provided they are of exceptional interest for readers. The case report consists of Abstract (unstructured), Introduction, Case Report, Discussion, Acknowledgements and References. Case reports must not exceed 1,000 words, 15 references and reasonable amount of tables and/or figures.

Letters to the Editor:

Letters could be of two types, either commenting on recently published articles or reporting cases, outbreaks, or original research. The former must be received within 2 months of publication of the article to which they refer and should be no longer than 500 words. The latter should contain no more than 1000 words with up to 10 references and 2 figures and/or tables. They should not be divided into sections.

Other:

Guest Editorial is solicited by the Editorial Board. National Reports or similar cases are accepted based on confirmation by Editorial Board.

2. **Submission**:

Papers submitted for publication should describe original work, not previously published elsewhere, totally or partly. Manuscripts must be submitted only in English and should be written according to sound grammar and proper terminology. Submission is only acceptable via Journal website : **http://ijph.tums.ac.ir**.

Manuscript must be accompanied by a covering letter to the Editor-in-Chief, including title and author(s) name and undertaking that it has not been published or submitted elsewhere.

The title page of the paper should only contain **the title, name(s), degree(s) and addresses (Tel, Fax, and Email) of the author(s).**

The manuscript should include: **Title**; **No author(s) name**; the **Abstract**; **Introduction**; **Materials & Methods**; **Results**; **Discussion**; **Acknowledgement, References, Tables and Figures**. **Please submit all aforementioned items in just one manuscript. Please do not send the PDF format.**

The Abstract (no more than 250 words) in structured format as Background, Methods, Results and Conclusion followed by 3 to 5 Keywords must be presented.

Tables in limited numbers should be submitted with the captions placed above. Do not submit tables as photograph. Place explanatory matters in footnotes, not in the heading.

Figures should be in limited numbers, with high quality art work and mounted on separate pages. The captions should be placed below.

The same data should not be presented in tables, figures and text, simultaneously.

3. **References**:

References in limited numbers and up-to-dated should be numbered consecutively as they occur in the text (number in parentheses). The references should observe the following style:

Article: Jarvis WR, Komshian SV (1995). Epidemiology of nosocomial fungal infections. *Clin Infect Dis*, 20 (6): 1526-30.

Chapter: Hillyer GV (1998). Immunodiagnosis of human and animal fasciolosis. In: *Fasciolosis*. Ed, JP Dalton. CABI Publishing, 1st ed. Oxon, Wallingford, UK, pp. 435- 48.

Book: Charmaz K (1991). *Good days, bad days: The self in chronic illness and time.* 2nd ed. New Brunswick: Rutgers University Press. New York.

Monograph on the Internet: Lundstedt S (2003). Analysis of PAHs and their transformation products in contaminated soil and remedial processes. University of Amsterdam, the Netherlands. Available from: *www.google.com*

Thesis: Mohammadi MM. Infant sleep and feeding [PhD thesis]. School of Public Health, Tehran University of Medical Sciences, Iran; 2002.

Note: If the authors have the article prepared using EndNote, we prefer to receive it.

4. **Abbreviations and symbols:**

Please use only standard abbreviations. Avoid using them in the title and abstract. The full term for which an abbreviation stands should precede its first use in the text unless it is a standard unit of measurement.

5. **Clinical trial registry:**

Reports of randomized clinical trials should present information on all major study elements, including the protocol, assignment of interventions (methods allocation to treatment groups), and the method of masking (blinding), based on the CONSORT Statement (http://www.consort-statement.org). Iranian articles for this sort should be registered first via (*www.irct.ir/*) because no RCT articles are accepted unless it contains the official registered code. Registration in the following trial registers is acceptable as well: http://www.actr.org.au/

http://www.clinicaltrials.gov/

http://isrctn.org/

http://www.trialregister.nl/trialreg/index.asp

http://www.umin.ac.jp/ctr

6. **Authorship Criteria:**

Authorship credit should be based only on substantial contributions to each of the three components mentioned below:

1. Concept and design of study or acquisition of data or analysis and interpretation of data;

2. Drafting the article or revising it critically for important intellectual content;

3. Final approval of the version to be published; and

4. Willingness to assume responsibility of the study.

Participation solely in the acquisition of funding or the collection of data does not justify authorship. General supervision of the research group is not sufficient contributor should have participated sufficiently in the work to take public responsibility for appropriate portions of the content of the manuscript.

7. **Reprint**:

No reprints are presented to authors. The Journal is open access and all authors may acquire their article full text free of charge through the web.

8. **Ethics:**

The relevant Ethics committee/ institution review boards of the respective institutions must approve the study. The study itself should follow the ethical standards of the Helsinki Declaration, as revised in 2013 (available at http://www.wma.net/en/30publications/10policies/b3/).

Ensure confidentiality of subjects by desisting from mentioning participants' names, initials or hospital numbers, especially reporting experiments on animals, indicate whether the institution's or a national research council's guide for, or any national law on the care and use Evidence for approval by a local Ethics Committee (for both human as well as animal studies) must be supplied by the authors on demand. IJPH will not consider any paper which is ethically unacceptable. The related items should be inserted under the 'Materials and Methods' section.

Protection of Patients' Rights to Privacy

Informed consent from the participants and from the parents or legal guardians of minors should be taken and stated in the study under the 'Materials and Methods' section.

Authors should remove patients' names from figures. Any data leading to direct recognize of the patient, strictly should be omitted.

Misconducts

IJPH is a member of COPE and follows its Best Practice Guidelines for Journal Editors. Plagiarism of text from a previously published manuscript by the same or another author is a serious publication offence. Small amounts of text may be used, but only where the source of the material quoted is clearly acknowledged and the text is inserted in quotation mark. If there is an allegation of plagiarism, scientific misconduct or fraud, IJPH will follow the recommendations of the COPE and ICMJE. The Journal reserves the right to report the allegations to the author's institution or any other agency.

Conflicts of interest

Submitting a manuscript must be accompanied with a statement from the authors disclosing all financial and personnel relationship that might bias their work, if any. Besides, they are requested to evident whether impending conflicts do or do not exist. A separate page should cover this proclamation and if there are further details, could be mentioned in covering letter. If an organization encompasses any financial interest in the outcome of the study, the authors are appealed to provide a declaration that have full access to all the data in the study and take complete responsibility for the integrity of the data and the accuracy of the data analysis.

9. **Peer review process:**

IJPH is a peer reviewed journal. All manuscripts will be acknowledged upon presenting to the Journal office, provided that all stated requirements are met. According to the policy of peer review in our Journal, a large extent of manuscripts are rejected through an in-house evaluation process based on a category of criteria including over flow of manuscripts, out of scope cases, poor outcome, local studies, clinical contents etc. This process takes no more than two weeks and the author(s) will be informed of the primary decision. The first stage passed manuscripts are sent to two or three reviewers. The whole review process depends on receiving referees' comments and revising the manuscripts based on these comments to the author. On receipt of the revised article from the author, and after final approving by referees, the letter of acceptance is issued to the author. Authors have the right to communicate to the editor if they do not wish their manuscript to be reviewed by a particular reviewer because of potential conflicts of interest. The author can also suggest the name of possible competent reviewers but it is up to the editor

to accept it. No article is rejected unless negative comments are received from at least two reviewers.

To assist the speed of peer review process, authors are requested to introduce four well-known experts with their contact details, but the Editor-in-Chief would be emancipated finally.

The revised version of the manuscript should be included with reply to referees' comments separately article to article. In addition, the changes should be marked as underlined or colored text in the article.

10.

Proofs:

Authors are sent galley proofs for checking the production after acceptance of the article. Proofs are sent by e-mail as Word files and considering that the Journal is published monthly, if for any reason, after 2 days, the Journal does not receive any reply, we consider the manuscript approved, and no changes will be acceptable after that. It is the authors' responsibility to check that all the text and data as contained in the page proofs are correct and suitable for publication. We request that authors pay particular attention to author's names and affiliations as it is essential that these details are accurate when the article is published. In this step, the authors absolutely, cannot add any authors or large sentences to the article, besides; they are not allowed to change the corresponding author.

After approving the galley proof no changes would be accepted and the responsibility would be on author(s) side.

11. **Copyright:**

Accepted manuscripts become the permanent property of the Journal and may not be reproduced, in whole or in part, without the written per-mission of the Editor.

12. **Page charges:**

There are no charges for publication in this Journal.

13. **Disposal of material**:

Once published, all copies of the manuscript, correspondence and artwork will be held for 6 months before disposal.

14. ***The Editorial Board of the journal, reserves the right to accept or reject the article in any stage and any time or delete a part of the text, tables or figures, if necessary.***

Copyright Notice

Accepted manuscripts become the permanent property of the Journal and **may not be reproduced, in whole or in part, without the written per-mission of the Editor.**

Privacy Statement

The names and email addresses entered in this journal site will be used exclusively for the stated purposes of this journal and will not be made available for any other purpose or to any other party.

Iranian Journal of Public Health allow the author(s) to hold the copyright without restrictions. Also the journal allow the author(s) to retain publishing rights without restrictions.

Manuscript 3 – Southern African Journal of Infectious Diseases Author Guidelines

From Southern African Journal of Infectious Diseases www.sajie.co.za accessed on 22 February 2015

Author Guidelines for Manuscript 3

Author Guidelines

Manuscripts submitted to the SAJID must be in the form of *Research Articles, Brief Reports, Clinical Case Studies, Correspondence, Reviews, State-of-the-Art Articles, Commentaries and Opinion Papers, Editorials* or *Supplement Articles.* The Journal welcomes the publication of *Guidelines, Conference Proceedings Newsletters or Press Releases,* and *Book Reviews.* Articles, Brief reports and Reviews are peer reviewed; other categories are reviewed by the Editors. Commentaries and Editorials are generally invited contributions, indicating the authors' identity, while manuscripts in the form of Reviews, and State-of-the-Art Articles may also be requested by the Editors.

All manuscripts must have conflict of interest and funding statements. When authors submit a manuscript, whether an article or a letter, they are responsible for disclosing all financial and personal relationships that might bias their work. To prevent ambiguity, authors must state explicitly whether potential conflicts do or do not exist. Authors should do so in the manuscript on a conflict-of-interest notification page that follows the title page.

Manuscripts describing research in human subjects or animals must indicate ethics clearance from appropriate research review committees. When reporting experiments on human subjects, authors should indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.

Articles describe original investigations at an acceptable degree of completion, constituting an advance in the field. Articles must not exceed 3500 words of text, without counting the abstract, references or legends, and illustrations and tables must be limited to the minimum necessary for clear and concise presentation. The abstract must either be structured, using *Background, Methods, Results,* and *Conclusions* as headings and comprising no more than 250 words, or unstructured with a 200 word limit. Articles are limited to a maximum of 7 insets (tables and figures combined) and 50 references.

Brief Reports present complete studies that are narrower in scope than those described in Articles or that present new developments. Manuscripts that are descriptive or primarily methodological in nature, or that describe in vitro chemotherapeutic studies should, in general, be submitted as Brief Reports. Brief Reports include an abstract (no more than 100 words) and are limited to a total of no more than 2000 words of text, a total of 2 inserts (tables or figures), and 15 references.

Correspondence (letters) must be submitted in reference to a previous publication in SAJID (within the previous 12 months), or relate to a topical matter in line with the interests of FIDSSA, PHASA or their affiliated societies. Please prepare the letter in manuscript format, including a title page. The letter must not exceed 750 words of text, 1 insert (table or figure) and 10 references.

Commentaries and Editorials are generally invited by the Editor and are overviews of articles in SAJID, or of other research in epidemiology or infectious diseases, or matters relating to public health and other issues of special interest to FIDSSA, PHASA or their associated societies. Unsolicited commentaries are also considered.

Reviews and *State-of-the-Art Articles* that are research oriented or fall within the fields of interests of FIDSSA, PHASA or any of their affiliated societies will be considered for publication by SAJID. Prospective authors of such manuscripts are advised to communicate with the Editor in advance to ensure that a specific contribution is deemed appropriate and timely. Manuscripts of Reviews and State-of-the-Art Articles will be peer-reviewed.

Reviewers

The Journal would encourage authors to supply the names of at least 2 potential reviewers for their manuscript, as well as to indicate any reviewers they would feel may have a potential conflict of interest with regard to their submission.

Supplements

Requirements for supplement manuscripts generally follow those for SAJID manuscripts, including conflict of interest and funding statements. Inquiries relating to suitability of topic, programme organisation, production and costs should be made to the Editor.

Evaluation of manuscripts

Review procedure. The Editor-in-Chief and Emeritus Editor screen all unsolicited manuscript submissions and some of these are rejected without further review. All other manuscripts are sent to a minimum of two outside experts for review. After receipt of the reviewers' reports, the Editor-in-Chief and the Emeritus Editor with administrative assistance of the Journal Secretary discuss the merits of the manuscripts and the Editor-in-Chief makes the final decision to accept, reject, or request revision of the manuscript. A request for revision does not guarantee ultimate acceptance of the revised manuscript

Related manuscripts. If there appears to be significant overlap between a manuscript submitted to SAJID and another submitted manuscript by the same authors to SAJID or another journal, the editors will take the matter up with the corresponding author, and based on the response, take appropriate action (ask for modification, or reject with detailed explanation). Further action may include informing the appropriate authority in the authors' resident institution and if overlapping is discovered after publication in SAJID, publishing an appropriate announcement to that effect in the journal.

DOCUMENT REQUIREMENTS

Checklist

The following are required for your manuscript to be processed:

- Covering letter
- Word count limits
- Conflict of interest statement
- Funding statement
- List of potential reviewers

Covering Letter

All manuscripts submitted to SAJID must be accompanied by a letter declaring that the manuscript has not been submitted or accepted for publication elsewhere. This letter must confirm and declare that all authors have seen and approved the content and have contributed significantly to the work. Authors should suggest potential unbiased reviewers who are qualified to review their manuscript. A covering letter must also accompany a revised submission and must address issues raised in the review process.

Manuscript Preparation

The SAJID complies with the Uniform Requirements for Manuscripts Submitted to Biomedical Journal Journals (*Ann Intern Med* 2000; 133:229-231 [editorial]; **http://www.icmje.org**, full text). Text, tables, references, and legends must be double- spaced. Italics should be used for genus and species names and for genes but not for in vivo, in vitro, in situ, et al., or other Latin-derived expressions. For layout of manuscript and appropriate style see a recent issue of SAJID.

Title page. On the title page, please supply a running head of not more than 40 characters and spaces, a title of not more than 160 characters and spaces, the names and affiliations of all the

authors, and word counts of the abstract and text. Each author's first name, subsequent initials and surname must be used.

Footnote page. Footnotes must include:

- Statement that authors either have or have not a commercial or other association that might pose a conflict of interest (e.g. pharmaceutical stock ownership, consultancy, advisory board membership, relevant patents, or research funding)

- Statement naming sources of financial support (including grant numbers)

- Name, date (month and year), and location (city, and country if not South Africa) of a meeting at which all or part of the information has been presented (include an abstract number, if available)

- Name, address, telephone and fax numbers, and e-mail address of the person to whom correspondence should be addressed

- Current affiliations and addresses for authors whose affiliations have changed since completion of the study

Abstract. The abstract for an Article may be structured with the headings Background, Methods, Results, and Conclusions (250-word limit) or unstructured (200-word limit). Abstracts of Brief Reports should be no more than 100 words. Whether structured or unstructured, the abstract must state the purpose of the research, the methods used, the results, and the conclusions. Do not cite references in the abstract. Include up to 10 key words, separate from the abstract. Please remember that the abstract is particularly useful for literature retrieval purposes.

Text. The text of Articles must be no longer than 3500 words, and that of Brief Reports no longer than 2000 words. The Methods section must include a statement that informed consent was obtained from patients or their parents or guardians, and human experimentation guidelines of the National Department of Health (http://www.doh.gov.za) or the South African Medical Research Council (MRC; http://www.sahealthinfo.org/ethics/index.htm) and /or those of the authors' institution(s) were followed in the conduct of clinical research or that animal experimentation guidelines (see MRC website above) were followed in animal studies.

References. Articles are generally limited to 50 references, Brief Reports to 15 references. Only works that have been published or accepted for publication can be included in the reference list. Unpublished observations by the authors (authors' unpublished data) personal communications (SP Stanley, personal communication), and manuscripts submitted for publication (J Odendaal, S Coovadia and J Radebe, submitted) should be mentioned parenthetically in the text Please number references in order of appearance; those cited only or first in tables or figures are numbered according to the order in which the table or figure is cited in the text. Example: If table 3 is cited in the text after reference 20, a new reference cited in table 3 will be reference 21.

References must follow the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org, full text). Provide all authors' (or editors') names when there are fewer than 7; for 7 or more, list the first 3 and add "et al." Titles of journals not listed in *Index Medicus* should be spelt out in full. Reference to a doctoral thesis or Master's dissertation should include the author, title, institution, location, year and publication information, if published. For online resources, include a URL and date accessed. Accuracy of references is the responsibility of the authors.

Examples of the proper format are as follows:

Sonnenberg P, Glyn Thomas R, Glynn JR, Shearer S, Godfrey-Faussett, Murray J. Clinical and radiological features of pulmonary disease due to culture-positive Mycobacterium tuberculosis or non-tuberculous mycobacteria in South African gold miners. South Afr J Epidemiol Infect 2005; 20: 130-135

Marin M, Nguyen HQ, Langidrik JR, et al. Measles transmission and vaccine effectiveness during a large outbreak on a densely populated island: Implications for vaccination policy. Clin Infect Dis 2006; 42: 315-319

Strebel PM, Papania MJ, Halsey NA. Measles vaccine. In: Plotkin SA, Orenstein WA, eds. Vaccines. 4th ed. Philadelphia: WB Saunders, 2004: 389-440.

Mothibeli KM, McGee L, Smith AM, Klugman KP. Molecular epidemiology of pneumococcal serotype 3 isolates.[abstract ID P56]. In: Programme and Abstract Book of the 1st Joint Congress of the Federation of Infectious Diseases Societies of Southern Africa (Sun City, North-West Province). Johannesburg: Presentations Graphics, 2005: 42.

World Health Organization. Initiative for vaccine research. Available at: http://www.who.int/vaccine_research/diseases/measles/en/. Accessed 1 February 2005.

Acknowledgment(s). The page preceding the references may include a statement thanking those who assisted substantially with work relevant to the study.

Statistical analysis. The statistical analyses used should be identified both in the text and in all tables and figures where the results of statistical comparison are shown.

Units of measure. All Data should be expressed in metric units; use of SI units is encouraged. Use °C for temperature.

Tables and figures. Articles are limited to a maximum of seven inserts (tables and figures combined), Brief Reports to a maximum of two inserts. Data should not be repeated in both a table and a figure. Abbreviations and acronyms used in tables and figures must be explained in the table footnotes and figure legends, even if already defined in the text.

Tables should be numbered in the order of mention in the text. Tables should be typed double-spaced throughout, with no vertical or internal rules. Footnotes and accompanying explanatory material should be kept to a minimum. Footnotes should be placed below the table and designated by superscript lowercase letters (listed in order of location when the table is read horizontally). Each column must have an appropriate heading describing the data in the column below, and units of measure must be clearly indicated. For further instructions on the preparation of tables in Word , consult the Special Instructions for Tables.

Figures should be also numbered in the order of mention in the text and should appear at the end of the manuscript and references. Your figures should be prepared in accordance with the Guidelines for Submission of Artwork. Letters, numbers, and symbols should be clear and of sufficient size to be legible when the figures are reduced. Photomicrographs should have internal scale markers. Figures reproduced from other publications must be accompanied by permission from the copyright holder. If the manuscript is accepted, the author will be required to send one complete set of glossy, hard-copy figures.

Figure legends should be double-spaced and appear on a separate page preceding the figures. Any abbreviations or symbols used but not defined in the figure itself must be defined in the legend.

Style. Authors are referred to the *American Medical Association Manual of style: A Guide for Authors and Editors* (9th ed., Williams& Wilkins, 1997) and the *Chicago Manual of Style* (15th ed., University of Chicago Press, 2003).

For commercially obtained products mentioned in the text, list the full names of manufacturers. Generic names of drugs and other chemical compounds should be used.

Nomenclature. SAJID recommends the latest widely accepted nomenclature, as set out in documents prepared by recognised international agencies e.g. the *International Journal of Systematic and Evolutionary Microbiology, Bergey's Manual of Determinative Bacteriology* (9th ed., revised, Williams& Wilkins, 1993), *Virus Taxonomy – The Classification and Nomenclature of Viruses: Sixth Report of the International Committee on Taxonomy of Viruses* (Springer-Verlag, 1995). The latter document also supplies standard abbreviations for virus species.

Clinical trials registration. All clinical trials must be registered in a registry that is electronically accessible to the public, free of charge. Registration should occur before patient enrolment and the registry's URL and the trial's registration number must be supplied at the end of the manuscript's abstract. For information on acceptable registries, consult the ICMJE Web site,

http://www.icmje.org . The National Library of Medicine's registry which is free and open to all investigators, generally meets with the requirements of journals for the publication of clinical trials.

MANUSCRIPT SUBMISSION

Procedure

Authors are advised to retain a copy of submitted manuscripts, including tables, figures and photomicrographs. The journal is not responsible for manuscripts lost or damaged.

All manuscripts must be submitted online at www.sajei.co.za. Register as an author, login in and click on **CLICK HERE TO FOLLOW THE FIVE STEP SUBMISSION PROCESS**. The covering letter must please be submitted as a supplementary file. For assistance to upload your manuscript or further instructions please contact Ms Robyn Marais at toc@sajei.co.za.

Editorial Committee

Editor-in-Chief
Professor Charles Feldman
E-mail address: Charles.Feldman@wits.ac.za

Emeritus Editor
Professor Hendrik J Koornhof
E-mail address: hendrik.koornhof@nhls.ac.za.

Journal Secretary
Ms Priscilla May
Southern African Journal of Infectious Diseases
National Health Laboratory Service
Private Bag X8
Sandringham 2131
E-mail address: priscillam@nicd.ac.za

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. The submission has not been previously published, nor is it before another journal for consideration (or an explanation has been provided in Comments to the Editor).
2. The submission file is in Microsoft Word, RTF document file format.
3. Where available, URLs for the references have been provided.
4. The text is one and a half-spaced; uses a 12-point font; employs italics, rather than

underlining (except with URL addresses); and all illustrations, figures, and tables are placed within the text at the appropriate points, rather than at the end.

5. The text adheres to the stylistic and bibliographic requirements outlined in the Author Guidelines, which is found in About the Journal.
6. The following is required for your manuscript to be processed:
   - o Covering letter
   - o Word count limits
   - o Conflict of interest statement
   - o Funding statement
   - o List of potential reviewers

Manuscript 4 – South African Family Practice Author Guidelines

Author guidelines for Manuscript 4

Submissions

- » Online Submissions
- » Author Guidelines
- » Copyright Notice
- » Privacy Statement

Online Submissions

Already have a Username/Password for South African Family Practice?
Go to Login

Need a Username/Password?
Go to Registration

Registration and login are required to submit items online and to check the status of current submissions.

Author Guidelines

Submissions can only be made online at www.safpj.co.za. Authors need to register online with the journal prior to submitting a manuscript. Once registered, simply log in and begin an easy 5 step process to upload your manuscript. All manuscripts must be submitted in MS Word®, Open Office, or RTF format using Times New Roman font size 10 and single-spacing. Headings must be in Bold.

The author must always retain a copy. All the named authors must have approved the final manuscript. Pages should be numbered consecutively in the lower right corner. Please note that the Original Research section will follow a ";print-short, web-long"; policy, which means that only the abstracts will be published in print, with the full article published on the web. Some review articles may also be published under these provisions.

The following contributions are accepted (word counts exclude abstracts, tables and references):

1. *Original research* (Between 1000 and 3500 words):

2. *Letters to the Editor* (Up to 400 words):
3. *Scientific Letters* (Less than 600 words): A short abstract is required (125-150 words) and should be structured under the following headings: background, methods, results and conclusion. One table or graph and not more than 5 references.
4. *Review/CPD articles* (Up to 1800 words): Most review articles are published as part of the continuous professional development (CPD) programme of SAFP. A scientific editor is appointed to approve topics, invite authors and to review the articles before they are independently peer-reviewed. All articles are reviewed by a family physician as well a topic specialist. Review articles outside the CPD programme are welcomed. Once accepted they may be published in full in the printed journal OR a 250 word abstract will be published in print with the full article available online.
5. *Opinions (Open Forum)* (Between 1000 and 3500 words).
6. *Editorials* (Between 600 - 800 words): Scientific editorials can be used to highlight progress in any scientific field related to family medicine.

Please consult the Section Policies for more details regarding CPD articles.

Format

Title page: All articles must have a title page with the following information and in this particular order: Title of the article; surname, initials, qualifications and affiliation of each author; The name, postal address, e-mail address and telephonic contact details of the corresponding author; at least 5 keywords. Please do not use capital letters only for headings and names, but stick to the normal use of capital letters.

Abstract. All articles should include an abstract. The structured abstract for an Original Research article should be between 200 and 250 words and should consist of four paragraphs labelled "Background, Methods, Results, and Conclusions".

Only the abstract of Original Research articles will be published in print, and the abstract with the full article will be published online. It should briefly describe the problem or issue being addressed in the study, how the study was performed, the major results, and what the authors conclude from these results.

The abstracts for other types of articles should also be no longer than 250 words and need not follow the structured abstract format.

Keywords. All articles should include keywords. Up to five words or short phrases should be used. Use terms from the Medical Subject Headings (MeSH) of Index Medicus when available and appropriate. Key words are used to index the article and may be published with the abstract.

Acknowledgements. In a separate section, acknowledge any financial support received or possible conflict of interest. This section may also be used to acknowledge substantial contributions to the research or preparation of the manuscript made by persons other than the authors.

References. Cite references in numerical order in the text, in **superscript** format. Do not use brackets. In the References section, references must be numbered consecutively in the order in which they are cited, not alphabetically.

The style for references should follow the format set forth in the ";Uniform Requirements for Manuscripts Submitted to Biomedical Journals"; prepared by the International Committee of Medical Journal Editors.

Abbreviations for **journal titles** should follow *Index Medicus* format. Authors are responsible for the accuracy of all references. Personal communications and unpublished data should not be referenced. If essential, such material should be incorporated in the appropriate place in the text. List all authors when there are six or fewer; when there are seven or more, list the first three, then ";et al.";

When citing URLs to web documents, place in the reference list, and use following format: Authors of document (if available). Title of document (if available). URL. (Accessed [date]).

The following are sample references:
1. London L, Baillie R. Notification of Pesticide Poisoning: Knowledge, Attitudes and Practices of Doctors in the Rural Western Cape. S A Fam Pract 1999;20(1):117-20.
2. FDA Talk Paper: http://www.fda.gov/bbs/topics/ANSWERS/2002/ANS01151.html (Accessed 04/10/2002).

Click here for more sample references.

Tables. Tables should be self-explanatory, clearly organised, and supplemental to the text of the manuscript. Each table should include a clear descriptive title on top and numbered in Roman numerals (I, II, etc) in order of its appearance as called out in text. Tables must me inserted in the correct position in the text. Authors should place explanatory matter in footnotes, not in the heading. Explain in footnotes all nonstandard abbreviations. For footnotes use the following symbols, in sequence: *,†,‡,§,||,,**,††,‡‡

Figures. All figures must be inserted in the appropriate position of the electronic document. Symbols, lettering, and numbering (in Arabic numerals e.g. 1, 2, etc. in order of appearance in the text) should be placed below the figure, clear and large enough to remain legible after the figure has been reduced. Figures must have clear descriptive titles.

Photographs and images: If photographs of patients are used, either the subject should not be identifiable or use of the picture should be authorised by an enclosed written permission from the subject. The position of photographs and images should be clearly indicated in the text. Electronic images should be saved as either jpeg or gif files. All photographs should be scanned at a high resolution (300dpi, print optimised). Provision is made to upload individual images on the website as *supplementary files*. Please number the images appropriately.

Permission. Permission should be obtained from the author and publisher for the use of quotes, illustrations, tables, and other materials taken from previously published works, which are not in

the public domain. The author is responsible for the payment of any copyright fee(s) if these have not been waived. The letters of permission should accompany the manuscript. The original source(s) should be mentioned in the figure legend or as a footnote to a table.

Review and action. Manuscripts are initially examined by the editorial staff and are usually sent to independent reviewers who are not informed of the identity of the author(s). When publication in its original form is not recommended, the reviewers' comments (without the identity of the reviewer being disclosed) may be passed to the first author and may include suggested revisions. Manuscripts not approved for publication will not be returned.

Ethical considerations. Papers based on original research must adhere to the Declaration of Helsinki on ";Ethical Principles for Medical Research Involving Human Subjects"; and must specify from which recognised ethics committee approval for the research was obtained.

Conflict of interest. Authors must declare all financial contributions to their work or other forms of conflict of interest, which may prevent them from executing and publishing unbiased research. [Conflict of interest exists when an author (or the author's institution), has financial or personal relationships with other persons or organizations that inappropriately influence (bias) his or her opinions or actions.]*
**Modified from: Davidoff F, et al. Sponsorship, Authorship, and Accountability. (Editorial) JAMA 2001: 286(10)*

The following declaration may be used if appropriate: ";I declare that I have no financial or personal relationship(s) which may have inappropriately influenced me in writing this paper.";

Submissions and correspondence. All submissions must be made online at www.safpj.co.za and correspondence regarding manuscripts should be addressed to:

The Editor, South African Family Practice, PO Box 14804, Lyttelton, 0140. Telephone: (012) 664 7460
General Facsimile: (012) 664 6276. href="mailto:editor@safpj.co.za"> editor@safpj.co.za

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. The submission has not been previously published, nor is it before another journal for consideration (or an explanation has been provided in Comments to the Editor).
2. The submission file is in Microsoft Word, Open Office or RTF document file format.
3. All URL addresses in the text (e.g., http://pkp.sfu.ca) are activated and ready to click.
4. The text is single-spaced; uses a 10-point font; employs italics, rather than underlining (except with URL addresses); and all tables and figures are placed within the text at the

appropriate points, rather than at the end.

5. The text adheres to the stylistic and bibliographic requirements outlined in the Author Guidelines, which is found in About the Journal.
6. Electronic images are saved as either jpeg or gif files. All photographs were scanned at a high resolution (300dpi, print optimised) and saved/numbered appropriately corresponding with the text.
7. All tracking changes in the document must have been accepted before sending to SA Fam Pract.
8. Have you asked a colleague or language expert to proofread your final manuscript?
9. All supplemantary files such as survey instruments or scanned photographs are separated from the main text and will be uploaded as supplementary files.
10. In the case of a research paper, prior approval has been obtained from a research ethics committee, and this fact is declared in the methods section of the manuscript.

Copyright Notice

Privacy Statement

The names and email addresses entered in this journal site will be used exclusively for the stated purposes of this journal and will not be made available for any other purpose or to any other party.

S Afr Fam Pract: ISSN (Print): 2078-6190, ISSN (Web): 2078-6204

Annexure G - Manuscript Submissions and Editor Decisions

Manuscript 1: Editor Decision

Gmail by Google

Dineo Pereko <dineopereko@gmail.com>

[JIDC] Editor Decision - ID#7329 - ID#7329

1 message

Ana Herrero Fresno <ahefr@sund.ku.dk> 23 September 2015 at 10:39
To: Mrs Dawn Dineo Pereko <dineopereko@gmail.com>
Cc: Martie S Lubbe <martie.lubbe@nwu.ac.za>, Sabiha Y Essack <essacks@ukzn.ac.za>

Mrs Dawn Dineo Pereko:

We have reached a decision regarding your submission to The Journal of Infection in Developing Countries, "Surveillance of Antibiotic Use in the private sector in Namibia using sales and claims data".

I would like to confirm that your article has been now accepted for publication and sent for copy-editing.

Sincerely,

Our decision is to:

Ana Herrero Fresno
Department of Veterinary Disease Biology, Veterinary Clinical Microbiology
Grønnegårdsvej 15
1870 Frb. C.

Phone: +45 353-32782
E-mail: ahefr@sund.ku.dk
ahefr@sund.ku.dk
The Journal of Infection in Developing Countries
http://www.jidc.org/

Manuscript 2: Submission Acknowledgement

Gmail by Google

Dineo Pereko <dineopereko@gmail.com>

[IJPH] Submission Acknowledgement

1 message

Dariush Farhud <ijph@tums.ac.ir> 17 July 2015 at 12:07
To: Mrs Dawn Dineo Pereko <dineopereko@gmail.com>

Mrs Dawn Dineo Pereko:

Thank you for submitting the manuscript, "Antibiotic Use and resistance in the private sector in Namibia" to Iranian Journal of Public Health. With the online journal management system that we are using, you will be able to track its progress through the editorial process by logging in to the journal web site:

Manuscript URL:
http://ijph.tums.ac.ir/index.php/IJPH/author/submission/10147
Username: dawnpereko

Please note that due to heavy flow of submitted articles, accepted articles will be published after 8-10 months.

If you have any questions, please contact me. Thank you for considering this journal as a venue for your work.

Dariush Farhud
Iranian Journal of Public Health

Dr MB Rokni
Editor
Iranian J Publ Health
Professor
PhD in Medical Parasitology
Member of WHO's Food borne disease Burden Epidemiology Reference Group (FERG)
P.O.BOX: 6446 Tehran 14155,IRAN
Telfax: +98 21 88950184

Manuscript 3: Editor Decision

Gmail by Google

Dineo Pereko <dineopereko@gmail.com>

[SAJID] #664 Public knowledge, attitudes and behaviour towards antibiotic usage in Namibia

2 messages

Dineo Pereko <dineopereko@gmail.com> 17 July 2015 at 14:15
To: Mrs Robyn Marais <toc@sajei.co.za>

Dear Mrs Marais,

On the 4th February 2015 I received an email regarding acceptance of this article for publication and that we would be contacted by the proofreader to finalise editing. To date we have heard nothing. Would you have any update?

Sincerely,

–
Dineo

Robyn Marais <pmarais@mweb.co.za> 24 July 2015 at 14:46
To: Dineo Pereko <dineopereko@gmail.com>

Dear Dineo

We only publish four issues per year and as the manuscripts are accepted they are published. We have many manuscripts that must be published. Your manuscript is currently scheduled for the Vol 30 No 4 (2015) issue of SAJID which will be published in December.

Kind regards

Mrs Robyn Marais

Title Operations Co-ordinator

T: 012 807 5440

C: 083 459 5580

F: 086 691 0918

From: Dineo Pereko [mailto:dineopereko@gmail.com]
Sent: Friday, July 17, 2015 3:15 PM
To: Mrs Robyn Marais <toc@sajei.co.za>
Subject: [SAJID] #664 Public knowledge, attitudes and behaviour towards antibiotic usage in Namibia

[Quoted text hidden]

[SAJID] #664 Public knowledge, attitudes and behaviour towards antibiotic usage in Namibia

Personal/Studies x

Mrs Robyn Marais <toc@sajei.co.za> 4 Feb

to me

Dear Mrs Pereko

Thank you for your revised manuscript, which has been accepted for publication. You will be contacted by our proofreader, in due course, to finalise the editing of the manuscript.

Thank you for supporting the South African Journal of Infectious Diseases.

Yours sincerely
Prof H Koornhof
Editor: SAJID

Email: toc@sajei.co.za

Southern African Journal of Infectious Diseases
http://www.sajei.co.za