Antibiotic use and resistance patterns in the Namibian private health sector

D D MOHULATSI
13031198
BPharm, MPH

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

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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*

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<td>Surveillance of antibiotic use in the private sector of Namibia using medicines claims and sales data</td>
<td>Journal of infectious diseases in developing countries</td>
<td>Accepted for publication (Refer to Annexure G)</td>
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<td>Public knowledge, attitudes and behaviour towards antibiotic usage in Windhoek, Namibia</td>
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<td>Antibiotic use in Namibia: prescriber practices for common community infections</td>
<td>South African family practice</td>
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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; 5.97 DID wholesale).
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 weerstandsbiedenheidspatrone 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 voorskrifpatrone, antibiotikagebruik en antibiotika weerstandsbiedenheidspatrone 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, voorskrifpatrone, verbruikersgedrag sowel as kennis van antibiotika te ondersoek. ’n Retrospektiewe ontleiding van antibiotika groothandel- en voorskrifesdata van ’n mediese versekeringsfonds-administrateur vir die tydperk 2008 tot 2011 is gebruik om tendense in antibiotikagebruik te kwantifiseer. Jaarlykske laboratorium antibiogramverslae vanaf 2005 tot 2011 is as sensitiwiteitsdata gebruik. Deursnee-opnames, gebaseer op self-geadministreerde vraelyste, is gebruik om voorskrifpraktyke en pasiëntkennis en -gedrag ten opsigt 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 vierjaarlystperk 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 voorskrifesdata wat vanaf die mediese versekeringsfonds-administrator 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 die 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 versekeringsadministrator 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 dieselde 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 griesimptome). 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 onderzoek en geïmplementeer moet word.
Sleutelwoorde: antibiotikagebruik, Namibië, voorskryfpatrone, weerstandsbiedenheidspatrone, 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.

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

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

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

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| 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 Perekò.

Prof M S Lubbe

Prof S Y Essack
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### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>ACT</td>
<td>Artemisinin containing therapies</td>
</tr>
<tr>
<td>ADR</td>
<td>Adverse Drug Reactions</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired immunodeficiency syndrome</td>
</tr>
<tr>
<td>AMR</td>
<td>Antimicrobial Resistance</td>
</tr>
<tr>
<td>APIC</td>
<td>Professionals in Infection Control and Epidemiology</td>
</tr>
<tr>
<td>APUA</td>
<td>Alliance for Prudent Use of Antibiotics</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Classifications</td>
</tr>
<tr>
<td>BRICS</td>
<td>Brazil, Russia, India, China and South Africa</td>
</tr>
<tr>
<td>CA-MRSA</td>
<td>Community Acquired - Methicillin Resistant <em>Staphylococcus Aureus</em></td>
</tr>
<tr>
<td>CAP</td>
<td>Community Acquired Pneumonia</td>
</tr>
<tr>
<td>CDC</td>
<td>Centres for Disease Control and Prevention</td>
</tr>
<tr>
<td>CPD</td>
<td>Continuing Professional Development</td>
</tr>
<tr>
<td>DDD</td>
<td>Defined Daily Dosage</td>
</tr>
<tr>
<td>DID</td>
<td>DDD/1000 population/day</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>ESAC</td>
<td>European Surveillance of Antimicrobial Consumption</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
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</tr>
<tr>
<td>GDP</td>
<td>Gross Domestic Product</td>
</tr>
<tr>
<td>HA-MRSA</td>
<td>Hospital Acquired - Methicillin Resistant <em>Staphylococcus Aureus</em></td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>HIVDR</td>
<td>HIV drug resistance</td>
</tr>
<tr>
<td>IDSA</td>
<td>Infectious Disease Society of America</td>
</tr>
<tr>
<td>INRUD</td>
<td>International Network for Rational Use of Drugs</td>
</tr>
<tr>
<td>MDR-TB</td>
<td>Multi-drug resistant tuberculosis</td>
</tr>
<tr>
<td>MIMS</td>
<td>Monthly Index of Medical Specialities</td>
</tr>
<tr>
<td>MoHSS</td>
<td>Ministry of Health and Social Services</td>
</tr>
<tr>
<td>MRSA</td>
<td>Methicillin Resistant <em>Staphylococcus Aureus</em></td>
</tr>
<tr>
<td>NAAR</td>
<td>Namibians against Antimicrobial Resistance</td>
</tr>
<tr>
<td>NAMAF</td>
<td>Namibia Association of Medical Aid Funds</td>
</tr>
<tr>
<td>NAPPI</td>
<td>National Pharmaceutical Product Index</td>
</tr>
<tr>
<td>NEMLIST</td>
<td>Namibia Essential Medicines Lists</td>
</tr>
<tr>
<td>NIAID</td>
<td>National Institute of Allergy and Infectious Diseases</td>
</tr>
<tr>
<td>NIP</td>
<td>Namibia Institute of Pathology</td>
</tr>
<tr>
<td>NMP</td>
<td>National Medicines Policy</td>
</tr>
<tr>
<td>NMRC</td>
<td>Namibia Medicines Regulatory Council</td>
</tr>
<tr>
<td>NWU</td>
<td>North-West University</td>
</tr>
<tr>
<td>PHC</td>
<td>Primary Health Care</td>
</tr>
</tbody>
</table>
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.,
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-Rasmussen, 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-sulfadoxide 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 policymakers, 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

<table>
<thead>
<tr>
<th>Empirical research objectives</th>
<th>Study phase</th>
<th>Article where reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identifying and/or evaluating data sources for the quantification of antibiotic usage patterns in ambulatory patients in the private health sector of Namibia</td>
<td>Phase 1</td>
<td>Surveillance of antibiotic use in the private sector in Namibia using claims and sales data. Journal: <em>The journal of infection in developing countries</em> – Manuscript accepted for publication.</td>
</tr>
<tr>
<td>Examining from the perceptions of the public their behaviour regarding antibiotics use in the community of Windhoek.</td>
<td>Phase 3</td>
<td>Public knowledge, attitudes and behaviour towards antibiotic usage in Windhoek, Namibia. Journal: <em>Southern African journal of infectious disease</em> Manuscript accepted for publication</td>
</tr>
</tbody>
</table>
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 between 1 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**

<table>
<thead>
<tr>
<th>Level</th>
<th>Definition</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Main anatomical group</td>
<td>J – Anti-infectives for systemic use</td>
</tr>
<tr>
<td>2</td>
<td>Pharmacological/therapeutic sub-group</td>
<td>J01 – Antibacterials for systemic use</td>
</tr>
<tr>
<td>3</td>
<td>Pharmacological subgroup</td>
<td>J01C – Beta-lactam antibacterials, penicillins</td>
</tr>
<tr>
<td>4</td>
<td>Chemical subgroup</td>
<td>J01CA – Penicillins with extended spectrum</td>
</tr>
<tr>
<td>5</td>
<td>Chemical substance</td>
<td>J01CA04 – Amoxicillin</td>
</tr>
</tbody>
</table>

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**

<table>
<thead>
<tr>
<th>Data element added</th>
<th>Medical aid claims database</th>
<th>Wholesale database</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIMS classification</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>ATC Classification</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Generic name</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Product category</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Route of administration</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Daily dosage</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Prescription duration</td>
<td>√</td>
<td>N/A</td>
</tr>
</tbody>
</table>
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)**

<table>
<thead>
<tr>
<th>Organism</th>
<th>Isolates</th>
<th>% susceptible isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. coli</em></td>
<td>203</td>
<td>21 32 70</td>
</tr>
<tr>
<td><em>K. pneumoniae</em></td>
<td>79</td>
<td>22 22 65</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>36</td>
<td>50</td>
</tr>
</tbody>
</table>

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: Antibiotic susceptibility testing procedure for stool Specimen
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:

\[ \bar{x} = \frac{\sum x_i}{n} \]

*Where:*

- \( \bar{x} \) = average
- \( \sum x_i \) = 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, Pearson’s 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

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Antibiotic class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition of cell wall synthesis</td>
<td>Beta-lactams,</td>
</tr>
<tr>
<td>Inhibition of protein synthesis</td>
<td>Aminoglycosides, tetracyclines, macrolides, lincosamides</td>
</tr>
<tr>
<td>Inhibition of DNA synthesis</td>
<td>Fluoroquinolones</td>
</tr>
<tr>
<td>Inhibition of RNA synthesis</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Competitive inhibition of folic acid synthesis</td>
<td>Sulfonamides, trimethoprim</td>
</tr>
</tbody>
</table>

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

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).


**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 *Neisseria gonorrhoeae* 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 difficile* 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 *Escherichia 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 *Escherichia 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).


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

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

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**

<table>
<thead>
<tr>
<th>Facility type</th>
<th>Public</th>
<th>Private</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitals</td>
<td>34</td>
<td>13</td>
</tr>
<tr>
<td>Primary health care clinics</td>
<td>265</td>
<td>75</td>
</tr>
<tr>
<td>Health centres</td>
<td>44</td>
<td>8</td>
</tr>
<tr>
<td>Private provider consulting rooms</td>
<td>N/A</td>
<td>557</td>
</tr>
<tr>
<td>Private pharmacies</td>
<td>N/A</td>
<td>75</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>333</td>
<td>844</td>
</tr>
</tbody>
</table>

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

**Table 2-5: Distribution of healthcare workers by sector**

<table>
<thead>
<tr>
<th>Category</th>
<th># registered 2006/2007</th>
<th>Public sector</th>
<th>Private sector</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Number</td>
<td>%</td>
</tr>
<tr>
<td>Doctors</td>
<td>774</td>
<td>216</td>
<td>28</td>
</tr>
<tr>
<td>Registered nurses</td>
<td>2,989</td>
<td>1,626</td>
<td>54</td>
</tr>
<tr>
<td>Enrolled nurses</td>
<td>2,761</td>
<td>1,884</td>
<td>68</td>
</tr>
<tr>
<td>Pharmacists</td>
<td>239</td>
<td>27</td>
<td>11</td>
</tr>
<tr>
<td>Pharmacist assistants</td>
<td>137</td>
<td>65</td>
<td>47</td>
</tr>
<tr>
<td>Social workers</td>
<td>250</td>
<td>76</td>
<td>30</td>
</tr>
</tbody>
</table>

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). 

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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 Pereko¹, 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. Essack², 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:

\[
\text{DDD/1000/day} = \left( \frac{\text{Total consumption in DDDs}}{\text{Total population covered} \times \text{Total days in the period of data collection}} \right) \times 1000.
\]

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 $V=$
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

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

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

<table>
<thead>
<tr>
<th>Antibiotic Group</th>
<th>ATC*</th>
<th>Claims Data</th>
<th>Wholesale Data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DDD</td>
<td>%</td>
<td>DDD</td>
</tr>
<tr>
<td>Penicillin</td>
<td>J01C</td>
<td>11.19</td>
<td>41.77</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>J01D</td>
<td>5.28</td>
<td>19.70</td>
</tr>
<tr>
<td>Macrolides</td>
<td>J01F</td>
<td>4.99</td>
<td>18.64</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>J01F</td>
<td>0.08</td>
<td>0.29</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>J01A</td>
<td>1.99</td>
<td>7.43</td>
</tr>
<tr>
<td>Quinolones</td>
<td>J01M</td>
<td>2.68</td>
<td>10.00</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>J01B</td>
<td>0.01</td>
<td>0.03</td>
</tr>
<tr>
<td>Other Beta lactams</td>
<td>J01D</td>
<td>0.49</td>
<td>1.83</td>
</tr>
<tr>
<td>Other</td>
<td>J01X</td>
<td>0.09</td>
<td>0.32</td>
</tr>
<tr>
<td>Total</td>
<td>26.78</td>
<td>100.00</td>
<td>32.0</td>
</tr>
</tbody>
</table>

*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)**

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

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
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References


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**

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<th>Antibiotics</th>
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<td>213</td>
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<td>240,107</td>
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<td><strong>TOTAL (N)</strong></td>
<td>604,334</td>
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<tr>
<td><strong>PERCENT (%)</strong></td>
<td>53.52</td>
<td>46.48</td>
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\( p < 0.0001 \)
Cramer’s \( V = 0.205 \)
**Table s2: Antibiotic use by age group**

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<tr>
<th>Antibiotic</th>
<th>Frequency</th>
<th>&lt; 12</th>
<th>≥12 - ≤18</th>
<th>≥ 18 to ≤ 45</th>
<th>≥ 45 - ≤ 65</th>
<th>&gt; 65</th>
<th>Total</th>
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<td>21,487</td>
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<td>840</td>
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<tr>
<td>Amoxycillin/Flucloxacili</td>
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<td>1,754</td>
<td>7,455</td>
<td>4,310</td>
<td>279</td>
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<td>268</td>
<td>18</td>
<td>869</td>
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</tr>
<tr>
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<td>3,881</td>
<td>2,413</td>
<td>106</td>
<td>9,700</td>
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<td>Moxifloxacin</td>
<td>133</td>
<td>232</td>
<td>5,308</td>
<td>5,699</td>
<td>970</td>
<td>12,342</td>
<td></td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>40</td>
<td>154</td>
<td>4,275</td>
<td>3,045</td>
<td>456</td>
<td>7,970</td>
<td></td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>22</td>
<td>105</td>
<td>4,176</td>
<td>3,241</td>
<td>232</td>
<td>7,776</td>
<td></td>
</tr>
<tr>
<td>Oxytetracycline</td>
<td>1</td>
<td>46</td>
<td>168</td>
<td>83</td>
<td>7</td>
<td>305</td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td>376</td>
<td>491</td>
<td>724</td>
<td>419</td>
<td>24</td>
<td>2,034</td>
<td></td>
</tr>
<tr>
<td>Piperacillin</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>6</td>
<td>4</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Procaine penicillin</td>
<td>118</td>
<td>42</td>
<td>154</td>
<td>74</td>
<td>4</td>
<td>392</td>
<td></td>
</tr>
<tr>
<td>Roxithromycin</td>
<td>7</td>
<td>45</td>
<td>481</td>
<td>464</td>
<td>39</td>
<td>1,036</td>
<td></td>
</tr>
<tr>
<td>Streptomycin</td>
<td>0</td>
<td>18</td>
<td>116</td>
<td>80</td>
<td>3</td>
<td>217</td>
<td></td>
</tr>
<tr>
<td>Telithromycin</td>
<td>20</td>
<td>202</td>
<td>3,649</td>
<td>3,085</td>
<td>236</td>
<td>7,192</td>
<td></td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>15,024</td>
<td>3,612</td>
<td>40,800</td>
<td>44,743</td>
<td>1,082</td>
<td>105,261</td>
<td></td>
</tr>
<tr>
<td>TOTAL (N)</td>
<td>252,324</td>
<td>75,188</td>
<td>458,668</td>
<td>319,581</td>
<td>23,292</td>
<td>1,129,053</td>
<td></td>
</tr>
<tr>
<td>PERCENT (%)</td>
<td>22</td>
<td>7</td>
<td>41</td>
<td>28</td>
<td>2</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

>p<0.0001
Cramer’s V = 0.0424
**Table s3: Antibiotics by dispenser and generic indicator**

<table>
<thead>
<tr>
<th>Dispenser</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doctor</td>
<td>516,780</td>
<td>45%</td>
</tr>
<tr>
<td>Pharmacist</td>
<td>612,440</td>
<td>54%</td>
</tr>
<tr>
<td>Total</td>
<td>1,129,220</td>
<td>100</td>
</tr>
</tbody>
</table>

**Antibiotics dispensed as generic by dispenser**

<table>
<thead>
<tr>
<th>Dispenser</th>
<th>N</th>
<th>Y</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doctor</td>
<td>117,043</td>
<td>392,972</td>
<td>510,015</td>
</tr>
<tr>
<td>Pharmacist</td>
<td>140,384</td>
<td>466,845</td>
<td>607,229</td>
</tr>
<tr>
<td>Total (N)</td>
<td>257,427</td>
<td>859,817</td>
<td>1,117,244</td>
</tr>
<tr>
<td>Percent (%)</td>
<td>23.05</td>
<td>76.96</td>
<td>100</td>
</tr>
</tbody>
</table>

*p< 0.0001
Cramer’s V = 0.1093

**Table s4: Top 10 antibiotics and their associated cost**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>2008 (N= R26,941,120)</th>
<th>2009 (N = R33,423,266)</th>
<th>2010 (N= R36,651,164)</th>
<th>2011 (N= R43,711,348)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin/Clavulanic acid</td>
<td>R6,386,213</td>
<td>23.70</td>
<td>R7,144,060</td>
<td>R9,210,120</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>R252,666</td>
<td>0.94</td>
<td>R277,172</td>
<td>R268,151</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>R1,658,627</td>
<td>6.16</td>
<td>R3,478,219</td>
<td>R4,496,379</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>R1,306,707</td>
<td>4.85</td>
<td>R1,262,629</td>
<td>R1,250,311</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>R1,043,787</td>
<td>3.87</td>
<td>R1,607,022</td>
<td>R1,861,870</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>R5,728,547</td>
<td>21.26</td>
<td>R8,928,472</td>
<td>R11,816,865</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>R1,200,562</td>
<td>4.46</td>
<td>R1,934,721</td>
<td>R2,115,987</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>R2,301,450</td>
<td>8.54</td>
<td>R3,216,891</td>
<td>R3,119,778</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>R708,616</td>
<td>2.63</td>
<td>R686,809</td>
<td>R550,878</td>
</tr>
<tr>
<td>Trimethoprim/Sulfa</td>
<td>R979,800</td>
<td>3.64</td>
<td>R744,401</td>
<td>R800,654</td>
</tr>
<tr>
<td>TOTAL</td>
<td>R21,566,975</td>
<td>80.05</td>
<td>R29,280,396</td>
<td>R35,490,993</td>
</tr>
</tbody>
</table>
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 Pereko³, 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. Essack⁴, 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 United 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.whoceo.no/act_ddd_index). The data were expressed as DDD/1000 population/day using the formula:

\[
\text{DDD/1000/day} = \frac{\text{Total consumption in DDDs}}{\text{Total population covered} \times \text{Total days in the period of data collection}} \times 1000.
\]

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

*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 2011. 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. Haemophilus spp. species showed sensitivity to all antibiotics except cotrimoxazole.

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**

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

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)

<table>
<thead>
<tr>
<th>Antibiotic use year</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity year</td>
<td>0.856</td>
<td>0.858</td>
<td>0.843</td>
</tr>
<tr>
<td>2010</td>
<td>0.056</td>
<td>0.058</td>
<td>0.153</td>
</tr>
</tbody>
</table>

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


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\textsuperscript{a}, Martie S. Lubbe\textsuperscript{a}, Sabiha Y. Essack\textsuperscript{b}\textsuperscript{6}

\textsuperscript{a}Medicine Usage in South Africa, Faculty of Health Sciences, School of Pharmacy, North-West University, Potchefstroom, South Africa

\textsuperscript{b} School of Health Sciences, University of KwaZulu-Natal, Durban, South Africa.

Running head: \textbf{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

\textbf{Word counts:} abstract 245 words; article 3500 words
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

<table>
<thead>
<tr>
<th>Statement</th>
<th>N</th>
<th>True (%)</th>
<th>False (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics kill viruses (n=419)</td>
<td>419</td>
<td>268 (64%)</td>
<td>15 (36%)</td>
</tr>
<tr>
<td>When I have a cold (sore throat, cough, runny/blocked nose, fever), I should always take an antibiotic to feel better (n= 420)</td>
<td>420</td>
<td>174 (41%)</td>
<td>246 (59%)</td>
</tr>
<tr>
<td>When I have a cold, I should get an antibiotic to prevent it from getting worse (n= 417)</td>
<td>417</td>
<td>194 (46%)</td>
<td>223 (54%)</td>
</tr>
<tr>
<td>When I visit a doctor sick enough with cold, I usually expect an antibiotic (n= 417)</td>
<td>417</td>
<td>183 (44%)</td>
<td>234 (56%)</td>
</tr>
<tr>
<td>Unnecessary use of antibiotics makes them ineffective (n=416)</td>
<td>416</td>
<td>301 (72%)</td>
<td>115 (28%)</td>
</tr>
</tbody>
</table>
Table 2: Association of demographic variables with statements

<table>
<thead>
<tr>
<th>Statement</th>
<th>Gender</th>
<th>Age</th>
<th>Medical Aid</th>
<th>Employment</th>
<th>Education</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$p$</td>
<td>$v$</td>
<td>$p$</td>
<td>$v$</td>
<td>$p$</td>
</tr>
<tr>
<td>Antibiotics kill viruses</td>
<td>0.05</td>
<td>-0.10</td>
<td>0.5</td>
<td>-0.07</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>0.13</td>
<td>0.6</td>
<td>0.0</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>0.02</td>
<td>0.14</td>
<td>0.5</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>When I have a cold, I should take antibiotics to get better quicker</td>
<td>0.34</td>
<td>0.05</td>
<td>0.00</td>
<td>0.16</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>0.16</td>
<td>0.2</td>
<td>0.0</td>
<td>0.15</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>0.07</td>
<td>0.00</td>
<td>0.0</td>
<td>0.15</td>
<td>0.50</td>
</tr>
<tr>
<td>When I have a cold, I should take antibiotics to prevent getting worse</td>
<td>0.23</td>
<td>0.05</td>
<td>0.00</td>
<td>0.15</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>0.15</td>
<td>0.1</td>
<td>0.0</td>
<td>0.15</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>0.20</td>
<td>0.09</td>
<td>0.0</td>
<td>0.20</td>
<td>0.1</td>
</tr>
<tr>
<td>When I visit a doctor sick enough with cold, I usually expect an antibiotic</td>
<td>0.53</td>
<td>0.03</td>
<td>0.12</td>
<td>0.09</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>0.09</td>
<td>0.1</td>
<td>0.0</td>
<td>0.12</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>0.20</td>
<td>0.09</td>
<td>0.0</td>
<td>0.20</td>
<td>0.1</td>
</tr>
<tr>
<td>Unnecessary use of antibiotics makes them ineffective</td>
<td>0.90</td>
<td>-0.01</td>
<td>0.00</td>
<td>0.16</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>-0.01</td>
<td>0.16</td>
<td>0.0</td>
<td>0.16</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>0.36</td>
<td>0.07</td>
<td>0.0</td>
<td>0.36</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>0.07</td>
<td>0.1</td>
<td>0.0</td>
<td>0.07</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>0.1</td>
<td>0.5</td>
<td>0.0</td>
<td>0.1</td>
<td>0.5</td>
</tr>
</tbody>
</table>

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%. 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. Studies have shown that antibiotic purchases without a prescription were mainly on
the advice of the pharmacist.\textsuperscript{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.\textsuperscript{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\textsuperscript{17,18} evidencing general misconceptions among the public regarding the use of antibiotics for common infections especially respiratory tract infections.\textsuperscript{13} These findings are in line with Velden \textit{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. 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%). Younger respondents (less than 30 years of age) were the ones who showed the least knowledge of the relationship between antibiotic overuse and the development of resistance. Similar finding where knowledge of resistance increased with age was reported by Belkina et al.

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%. 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.
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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
Antibiotic use in Namibia: prescriber practices for common community infections

Dawn D Pereko1, Martie S Lubbe2 & Sabiha Y Essack2

1 Medicine Usage in South Africa, Faculty of Health Sciences, School of Pharmacy, North-West University, Potchefstroom, South Africa
2 School of Health Sciences, University of KwaZulu-Natal, Durban, South Africa

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To link to this article: http://dx.doi.org/10.1080/20786190.2015.1024021

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Antibiotic use in Namibia: prescriber practices for common community infections

Dawn D Pereiro*, Martie S Lubbe* and Sabine Y Esack**

*School of Health Sciences, University of KwaZulu-Natal, Durban, South Africa
**Corresponding author, email: dina.pereiro@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 21% respectively). Common practice in managing common infections, with the exception of chronic otitis media, cystitis and gonorrhoea, is to treat empirically. The most prescribed 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.

Conclusions: 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 sensitive 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.
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 6.1.2 (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 \( (p < 0.05) \). 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 \( (\chi^2) \) was used to determine whether a statistically significant association exists between proportions of two or more groups. Cramer’s \( V \) was used to test the practical significance of this association (with Cramer’s \( V \geq 0.3 \) 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 35 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 over-prescribing 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 antibiotics choices with the first-line antibiotic recommended in the national STG guideline.

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 28% of
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 3 strategies suggested by respondents were: provider education (41%), regular updates of local sensitivity data (35%), patient education (26%), antibiotic use (regulation and treatment guidelines) (18%). Other strategies included regular updates on prescription standards, 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 third National Medicine Use survey conducted among 1,313 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 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 prescribing practices of clinicians in Namibia.

Our study achieved a response rate of 100%, which is comparable and in some instances higher than the response rate reported by others.

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 (STG) 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; others reported that younger doctors were more likely to prescribe antibiotics than older doctors.

Similarly, some authors reported that doctors with fewer years of experience were more likely to prescribe antibiotics than their counterparts with longer experience, while others reported the opposite. 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. Similarly, looking at other studies we would have expected to find variations in prescribing practices based on qualifications and region of practice.

For all listed infections, doctors treat empirically. This is consistent with literature findings, which stated that fear was one of the factors influencing behaviour. In these studies, doctors generally reported fear of the development of serious infections.
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.\(^{41,43}\)

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 a review of antibiotic consumption reported in other studies of different methodologies.\(^{44,45}\)

For all infections, the reported preferred choice 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.\(^{41}\) 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 99% 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%).\(^{46}\) Local laboratory data show only 66% 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 pseudomonas. 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 89% sensitivity to amoxicillin and 99% 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 unexplained 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 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 biannual sensitivity data made available by the private laboratory in Namibia. This lack of guidelines has been cited by others as a factor influencing practice.\(^{47}\) 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.\(^{48}\) 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 soon as 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. "offending prescription" in this study was observed that 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.\(^{41,42}\) A study in Brazil found that physicians generally underestimated the prevalence of resistance in their area.\(^{42}\) Such underestimation could lead to patients being prescribed ineffective antibiotics. This was proven 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 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\(^ {49}\) in this study, we observed that respondents unnecessarily prefer broad-spectrum to effective narrow-spectrum antibiotics, which could lead to antibiotic resistance selection pressure. Dumps and colleagues also noticed similar preference in their study in Latvia.\(^ {41}\) 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.\(^ {42}\) Similarly, doctors in Scotland and France reported finding the strategy of restricting prescriptions most helpful.\(^ {41}\) Guidelines would thus 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.\(^ {41,42,43,44}\) Others have also indicated that while there may be international guidelines, local guidelines are most preferable.\(^ {41,42}\) 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.\(^ {41}\) 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 emphasizes 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 practices 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 STIs 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, this 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.

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References
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% increase in 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 (Autu 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.
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Annexures

Annexure A – Letter to the laboratory
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 Perekó

Prof. Martie S. Lubbe
Leader: Medicine Usage in South Africa
School of Pharmacy
North-West University
Potchefstroom Campus
Potchefstroom
2520
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
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
lkpharmacy@lway.na

We thank you for your time and your assistance.
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: ____________________
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 the 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 [ ] Date of Birth (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 [ ]
   - Bought from pharmacy (no prescription) [ ]
   - Got from friend [ ]
   - Had some left over at home [ ]

Page 1 of 2
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

<table>
<thead>
<tr>
<th>Statement</th>
<th>True</th>
<th>False</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Antibiotics kill viruses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. When I have a cold, I should take antibiotics to get better quicker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. When I have a cold, I should take antibiotics to prevent getting worse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. When I visit a doctor sick enough with cold, I usually expect an antibiotic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>e. Unnecessary use of antibiotics makes them ineffective</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

YOU HAVE JUST FINISHED THE SURVEY..............THANK YOU VERY MUCH.
We are very appreciative of your time in completing this survey.
OPNAME OOR DIE KENNIS VAN ANTIBIOTIKA-GEBRUIK ONDER AMBULANTE PASIËNTIN DIE PRIVATSEKTOR VAN NAMIBIÉ

INLEIDING:

Die snelle ontwikkeling en verspreiding van weerstand van bakterië 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 Namibié 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 **een** verpligtig 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 teruggespoort 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 □
   - Tersiële opleiding □

II. KENNIS VAN ANTIBIOTIKA:

6. Het jy in die afgelope jaar antibiotika gebruik? Ja □ Nee □
7. Hoe het jy die antibiotika gekry? (Merk meer as een indien nodig)
   - Voorskryf deur dokter □
   - Gekoop by apotek (geen voorskrif) □
   - By vriend gekry □
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 genees is verkeerd met jou (diagnose)?

10. Het jy die dokter vir 'n antibiotikum gevra? Ja□ Nee□

11. Is jy aanwysings gegaan van hoe om die antibiotikum te gebruik? Ja□ Nee□

12. Wanneer het jy opgehou om jou antibiotic te gebruik?
   - toe jy beter gevoel het □
   - toe die antibioticum klaar was □

13. Waar kry jy inligting oor antibiotika? Noem 3 bronse indien van toepassing.
   a. □
   b. □
   c. □

13. Dui aan of die volgende stellings waar of vals is:

<table>
<thead>
<tr>
<th>Stelling</th>
<th>Waar</th>
<th>Vals</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Antibiotika dood virusse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. As ek verkou het, moet ek antibiotika gebruik om gower pasend te word</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. As ek verkou het, moet ek antibiotika gebruik om te keer dat dit erger word</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. As ek siek genoeg aan verkou is en 'n dokter spreek, verwag ek gewoonlik 'n antibiotikum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>e. Onnodige gebruik van antibiotika maak hulle oneffektief</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

JY HET PAS DIE OPNAME VOLTOOI...................BAIE DANKIE.
Ons het hê waardeering vir die tyd wat jy afgestaan het om hierdie opname te voltoo.
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.

1. 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?
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.

<table>
<thead>
<tr>
<th>Infection</th>
<th>Do Routine Laboratory Culture</th>
<th>Laboratory Culture when Empirical Treatment Fails</th>
<th>Antibiotic / Antimicrobial Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Acute pharyngitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute otitis media</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic otitis media</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute sinusitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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/cini_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 registries that meet the ICMJE guidelines are available at [http://www.icmje.org/flow.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.

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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.

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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.

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**References**

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M. Jones (personal communication, August 03, 2012) finds the project meets several criteria ...

Professor Ahmad in an email to the author gave details of her clinical experience with this treatment (N. M. Ahmad, personal communication, January 12, 2013).

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Manuscript 2 – Iranian Journal of Public Health Author Guidelines
Iranian Journal of Public Health Author Guidelines

Author Guidelines

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JAMA 2001: 286(16)

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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](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
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Annexure G - Manuscript Submissions and Editor Decisions

Manuscript 1: Editor Decision
275

[JIDC] Editor Decision - ID#7329 - ID#7329
1 message

Ana Herrera Fresno <ahefr@sund.ku.dk> 23 September 2015 at 10:39
To: Mrs Dawn Dineo Peroko <dineoperoko@gmail.com>
Cc: Martie S Lubbe <martie.lubbe@nwu.ac.za>, Sabiha Y Essack <essack@sukzn.ac.za>

Mrs Dawn Dineo Peroko:

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,

Ana Herrera Fresno
Department of Veterinary Disease Biology, Veterinary Clinical Microbiology
Grennegardsvej 15
1870 Frihøje

Phone: +45 353-32782
E-mail: ahefr@sund.ku.dk
ahefr@sund.ku.dk
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Manuscript 2: Submission Acknowledgement
[IJPH] Submission Acknowledgement

1 message

Dariush Farhud <ijph@tums.ac.ir> 17 July 2015 at 12:07
To: Mrs Dawn Dineo Perekoko <dineoperekoko@gmail.com>

Mrs Dawn Dineo Perekoko:

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: dawnperekoko

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

---
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Professor
PhD in Medical Parasitology
Member of WHO's Food borne disease Burden Epidemiology Reference Group (FERG)
P.O.BOX: 8448 Tehran 14155,IRAN
Tel/fax: +98 21 88850184
Manuscript 3: Editor Decision
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>
To: Dineo Pereko <dineopereko@gmail.com>

24 July 2015 at 14:46

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@saaj.co.za>
Subject: [SAJID] #664 Public knowledge, attitudes and behaviour towards antibiotic usage in Namibia

[Quoted text hidden]
Mrs Robyn Marais <toc@saje.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 Koomhof
Editor: SAJID

Email: toc@saje.co.za

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