Antibiotic usage in South Africa: A longitudinal analysis of medicine claims data

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Finally brothers, whaterver is true, whatever is honourable, whatever is just, whatever is lovely, whatever is commendable, if there is any excellence, if there is anything worthy of praise, think about these things.

Phlippians 4:8.

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List of acronyms and abbreviations

A

AMR	Antimicrobial resistance
ATC	Anatomical Therapeutic Chemical

B

BSAC	British Society for Antimicrobial Chemotherapy

C

CAP	Community Acquired Pneumonia
CDC	Centres for Disease Control
CMS	Council for Medical Schemes
CSF	Cerebro-spinal fluid

D

DDD	Defined Daily Dose
DHP	Dehydropeptidase
DID	Defined Daily Dose per 1 000 Inhabitants per Day
DNA	Deoxyribonucleic acid

E

ECDC	European Centre for Disease Control
ESAC	European Surveillance on Antibiotic Consumption
ESGAP	European Study Group on Antibiotic Policies

F

FIDSSA	Federation of Infectious Diseases Societies of South Africa

G

GABA	Gaba-amino-butyric acid
GARP	Global Antibiotic Resistance Partnership
GERM-SA	Group for Enteric Respiratory and Meningeal disease Surveillance in South Africa
GI	Gastro – intestinal

List of acronyms and abbreviations (continued)

H

HPCSA	Health Professions Council of South Africa

I

IMS	Intercontinental Marketing Services

K

kg	kilogram

L

LRTI	Lower respiratory tract infection

M

max.	maximum
MDR	Multidrug resistant
mg	milligram
MIMS	Monthly Index of Medical Specialties
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*

N

NASF	National Antibiotic Surveillance Forum

P

PBM	Pharmaceutical Benefit Management
PDD	Prescribed Daily Dose
PMQR	Plasmid-mediated Quinolone Resistance

Q

QRDR	Quinolone Resistant Determining Region

R

RDD	Recommended Daily Dose
RNA	Ribonucleic acid
RTI	Respiratory tract infection

List of acronyms and abbreviations (continued)

S

SAS	Statistical Analyses System
STI	Sexually Transmitted Infections

T

TB	Tuberculosis

U

UTI	Urinary tract infection

V

VAP	Ventilator Associated Pneumonia

W

WHO	World Health Organization

Abstract and keywords

Antibiotic usage in South Africa: A longitudinal analysis of medicine claims data

The main aim of the study was to determine the prescribing patterns of antibiotics with an emphasis on fluoroquinolones in the private health sector of South Africa. The empirical study followed a quantitative, descriptive, observational method using retrospective, longitudinal medicine claims data provided by a nationally representative Pharmaceutical Benefit Management company (PBM) from 1 January 2005 to 31 December 2012. Penicillins, cephalosporins, carbapenems, aminoglycosides, chloramphenicol, fluoroquinolones, macrolides, tetracyclines, sulphonamides and trimethoprim were considered in the study.

A total of 5 155 262 (44.8%) patients received at least one antibiotic prescription out of the total number of registered beneficiaries included in the database. The average number of antibiotic prescriptions per patient per year ranged from 2.22 ± 1.89 (95% CI 2.22-2.22) in 2005 to 1.98 ± 1.62 (95% CI 1.98-1.99) in 2012. The number of antibiotics per prescription per year remained fairly constant at 1.05 ± 0.19 (95% CI 1.05-1.05) in 2005 to 1.06 ± 0.21 (95% CI 1.06-1.06) in 2012. The prevalence of patients receiving antibiotic prescriptions decreased from 46.1% (n = 789 247) in 2005 to 38.2% (n = 480 159) in 2012. Antibiotics were mostly prescribed for females (54.9%, n = 2 831 686) and in patients aged 0 to 18 years (26.5%, n = 1 366 824) and least in patients above 65 years (9.5%, n = 490 496). The prevalence of patients receiving antibiotic prescriptions was highest in Gauteng (41.9%, n = 2 159 360) and lowest in the Northern Cape (1.7%, n = 87 720). Antibiotics were mostly prescribed during the winter period. Penicillins were the most prescribed antibiotics (43%) and carbapenem the least (0.1%) out of the total number of antibiotics claimed. No practically significant association was found between antibiotic prescribing and gender, age, province and season.

A total of 1 983 622 prescriptions for fluoroquinolones were claimed in patients older than 18 years. The average number of fluoroquinolone prescriptions per patient per year ranged from 1.45 ± 0.92 (95% CI 1.44-1.45) in 2005 to 1.31 ± 0.71 (95% CI 1.31-1.32) in 2012. The highest prevalence of fluoroquinolone prescribing was observed in females (64.1%, n = 850 253) and in patients between 45 and 65 years (38.6%, n = 511 542). The total fluoroquinolone use by the study population decreased from 2.85 DID in 2005 to 2.41 DID in 2012. Norfloxacin was the only first-generation fluoroquinolone prescribed. The second-generation fluoroquinolones accounted for more than 50% of the total DID, with ciprofloxacin being the most used active ingredient in this generation. Moxifloxacin was the most prescribed third-generation fluoroquinolone; its use ranging from 0.51 DID in 2005 to 0.44 DID in 2012.

Between 2005 and 2012, a total of 57 325 prescriptions for fluoroquinolones were claimed by patients 18 years and younger. The prevalence of patients receiving fluoroquinolone prescriptions decreased from 3.6% (n = 8 329) in 2005 to 2.9% (n = 3 310) in 2012. Fluoroquinolones were mostly prescribed to females and in patients between 12 and 18 years. In all age groups, prescribing was mainly done by general medical practitioners. Ciprofloxacin was the most prescribed fluoroquinolone, followed by levofloxacin.

In conclusion, this study established estimates on the prevalence of antibiotic prescribing covering an eight-year period. Secondly, baseline estimates for fluoroquinolone prescribing in adults using the ATC/DDD methodology were determined. Fluoroquinolone prescribing patterns in children and adolescents were determined, with specific reference to the comparison between the prescribed daily and recommended daily dosages in the different age groups and by prescribers' specialties.

Keywords: antibiotics, fluoroquinolones, prescription claim database, trends, use, longitudinal, patterns, children, adults, private health sector, South Africa

Uittreksel en trefwoorde

Antibiotika-gebruik in Suid-Afrika: ’n Longitudinale ontleding van medisyne-eisedata

Die hoofdoel van die studie was om die voorskryfpatrone van antibiotika, met ’n klem op fluoorkinolone, in die private gesondheidsektor van Suid-Afrika, te bepaal. Die empiriese studie het ’n kwantitatiewe, beskrywende navorsingsontwerp gebruik deur van retrospektiewe, longitudinale medisyne-eisedata, verkry vanaf ’n nasionaal verteenwoordigende Farmaseutiese Voordelebestuursmaatskappy, vir die tydperk 1 Januarie 2005 tot 31 Desember 2012, gebruik te maak. Penisilline, kefalosporiene, karbapeneme, aminoglikosiede, chlooramfenikol, fluoorkinolone, makroliede, tetrasikliene, sulfoonamiede en trimetoprim is tydens die studie in ag geneem.

Altesaam 5 155 262 (44.8%) pasiënte, uit die totale aantal geregistreerde begunstigdes in die databasis, het ten minste een antibiotikumvoorskrif ontvang. Die gemiddelde aantal antibiotikumvoorskrifte per pasiënt per jaar het gewissel tussen 2.22 ± 1.89 (95% CI 2.22-2.22) in 2005 en 1.98 ± 1.62 (95% CI 1.98-1.99) in 2012. Die aantal antibiotika per voorskrif per jaar het redelik konstant gebly op 1.05 ± 0.19 (95% CI 1.05-1.05) in 2005 tot 1.06 ± 0.21 (95% CI 1.06-1.06) in 2012. Die voorkoms van pasiënte wat antibiotikumvoorskrifte ontvang het, het van 46.1% (n = 789 247) in 2005 tot 38.2% (n = 480 159) in 2012 afgeneem. Antibiotika is meestal vir vroue (54.9 %, n = 2 831 686) en in pasiënte tussen die ouderdomme van 0 en 18 jaar (26.5%, n = 1 366 824) voorgeskryf. Antibiotikumvoorskrifte vir pasiënte ouer as 65 jaar (9.5%, n = 490 496) was die minste. Die voorkoms van pasiënte wat antibiotikumvoorskrifte ontvang het, was die hoogste in Gauteng (41.9%, n = 2 159 360) en die minste in die Noord-Kaap (1.7%, n = 87 720). Antibiotika is meestal in die winter voorgeskryf. Uit die totale aantal antibiotika geëis, was penisillien die mees voorgeskrewe antibiotikum (43%) en karbapenem die minste (0.1%). Daar was geen prakties betekenisvolle assosiasie tussen antibiotikum voorgeskryf en geslag, ouderdom, provinsie, en seisoen nie.

Altesaam 1 983 622 fluoorkinolienvoorskrifte was geëis vir pasiënte ouer as 18 jaar. Die gemiddelde aantal fluoorkinolienvoorskrifte per pasiënt per jaar het gewissel tussen 1.45 ± 0.92 (95% CI 1.44-1.45) in 2005 en 1.31 ± 0.71 (95% CI 1.31-1.32) in 2012. Die hoogste voorkoms van fluoorkinolienvoorskrifte is waargeneem in vroue (64.1% n = 850 253) en in pasiënte tussen 45 en 65 jaar (38.6%, n = 511 542). Totale fluoorkinolienverbruik deur die studiebevolking het van 2.85 DID in 2005 tot 2.41 DID in 2012 afgeneem. Norfloksasien is die enigste eerste-generasie-fluoorkinolien wat voorgeskryf is. Die tweede-generasie-fluoorkinolone was

verantwoordelik vir meer as 50% van die totale DID, met siprofloksasien as die mees verbruikte aktiewe bestanddeel in hierdie generasie. Moxifloxacin was die mees voorgeskrewe derde-generasie-fluoorkinolien; verbruik het gewissel tussen 0.51 DID in 2005 en 0.44 DID in 2012.

Tussen 2005 en 2012 is altesaam 57 325 fluoorkinolienvoorskrifte deur pasiënte 18 jaar en jonger geëis. Die voorkoms van pasiënte wat fluoorkinolienvoorskrifte ontvang het, het van 3.6% (n = 8 329) in 2005 tot 2.9% (n = 3 310) in 2012 afgeneem. Fluoorkinolone is meestal vir vroue en pasiënte tussen 12 en 18 jaar, voorgeskryf. Algemene mediese praktisyns was vir die meerderheid van voorskrifte in alle ouderdomsgroepe verantwoordelik. Siprofloksasien, gevolg deur levofloksasien, was die mees voorgeskrewe fluoorkinolone.

Ter samevatting het hierdie studie beramings rakende die voorkoms van die voorskryf van antibiotika oor ’n agt jaar-periode bepaal. Tweedens is basislynberamings vir die voorskryf van fluoorkinolone in volwassenes met behulp van die ATC/DDD-metode bepaal. Fluoorkinoloonvoorskryfpatrone in kinders en tieners is bepaal, met spesifieke verwysing na die vergelyking tussen die voorgeskrewe daaglikse en aanbevole daaglikse dosisse in die verskillende ouderdomsgroepe en voorskrywerspesialiteite.

Trefwoorde: antibiotika, fluoorkinolone, medisyne-eisedatabasis, tendense, verbruik, longitudinaal, patrone, kinders, volwassenes, private gesondheidsektor, Suid-Afrika

Preface

This study was presented in article format. Three manuscripts were submitted for publication in the following journals:

- Southern African journal of infectious diseases (*submitted*)
- Journal of antimicrobial chemotherapy (*prepared*)
- Biomedical central paediatrics (*prepared*)

The chapters in this dissertation are outlined as follows:

- Chapter 1 provides a comprehensive background to the study, followed by the research method used.
- Chapter 2 is the literature review, focusing on antibiotics (brief summary on the mechanism of action, clinical uses and adverse effects of the various sub-pharmacological groups), fluoroquinolones (mechanism of action, clinical uses, adverse effects, use in paediatrics, and potential drug interactions); antimicrobial resistance; antibiotic usage patterns globally; and interventions to promote rational antibiotic use.
- Chapter 3 consists of the results and discussions section of the dissertation in the form of manuscripts.
- Chapter 4 is the conclusion, recommendations and limitations of the study.
- The annexures and references will be at the end.

The co-authors mentioned in the manuscripts were the supervisor and co-supervisors during the study period. The manuscripts that formed part of the dissertation were done upon their approval. The contributions of each author are subsequently outlined.

Authors' contributions (Study and manuscript 1)

The contribution of each author for manuscript 1 entitled **"Antibiotic prescribing patterns in the South African private health sector (2005-2012)"** is provided below:

Author	Role in the study
Ms WE Agyakwa	Literature review Planning and designing the manuscript Data and statistical analyses Interpretation of results Writing of dissertation
Prof MS Lubbe (Supervisor)	Supervision of concept of study and manuscript Data and statistical analysis Supervision on writing of manuscript Reviewing the manuscript carefully for final approval
Dr JR Burger (Co-supervisor) Dr NL Katende-Kyenda (Co-supervisor)	Co-supervision of concept of study and manuscript Data and statistical analyses Supervision on writing of manuscript Reviewing the manuscript carefully for final approval
Ms M Cockeran (Statistician)	Verified all results from statistical analyses

The following statement provided by the co-authors confirms their roles in the study and their permission that the manuscript may form part of the dissertation.

I declare that I have approved the above-mentioned manuscript and that my role in this study, as indicated above, is a representation of my actual contribution, and I hereby give my consent that it may be published as part of the MPharm study of *WE Agyakwa*.

……..
Prof MS Lubbe

……
Dr JR Burger

……
Dr NL Katende-Kyenda

……
Ms M Cockeran

Authors' contributions (Study and manuscript 2)

The contribution of each author for manuscript 2 entitled **"Fluoroquinolone utilisation patterns in adults in the private health sector of South Africa (2005-2012)"** is provided below:

Author	Role in the study
Ms WE Agyakwa	Literature review Planning and designing the manuscript Data and statistical analyses Interpretation of results Writing of dissertation
Prof MS Lubbe (Supervisor)	Supervision of concept of study and manuscript Data and statistical analysis Supervision on writing of manuscript Reviewing the manuscript carefully for final approval
Dr JR Burger (Co-supervisor) Dr NL Katende-kyenda (Co-supervisor)	Co-supervision of concept of study and manuscript Data and statistical analyses Supervision on writing of manuscript Reviewing the manuscript carefully for final approval
Ms M Cockeran (Statistician)	Verified all results from statistical analyses

The following statement provided by the co-authors confirms their roles in the study and their permission that the manuscript may form part of the dissertation.

I declare that I have approved the above-mentioned manuscript and that my role in this study, as indicated above, is a representation of my actual contribution, and I hereby give my consent that it may be published as part of the MPharm study of *WE Agyakwa*.

……..
Prof MS Lubbe

……
Dr JR Burger

……
Dr NL Katende-Kyenda

……
Ms M Cockeran

Authors' contributions (Study and manuscript 3)

The contribution of each author for manuscript 3 entitiled **"Prescribing patterns of fluoroquinolones in children and adolescents in the private health sector of South Africa (2005 – 2012)"** is provided below:

Author	Role in the study
Ms WE Agyakwa	Literature review Planning and designing the manuscript Interpretation of results Writing of dissertation
Prof MS Lubbe (Supervisor)	Supervision of concept of study and manuscript Data and statistical analysis Data and statistical analyses Supervision on writing of manuscript Reviewing the manuscript carefully for final approval
Dr JR Burger (Co-supervisor) Dr NL Katende-kyenda (Co-supervisor)	Co-supervision of concept of study and manuscript Data and statistical analyses Supervision on writing of manuscript Reviewing the manuscript carefully for final approval
Ms M Cockeran (Statistician)	Verified all results from statistical analyses

The following statement provided by the co-authors confirms their roles in the study and their permission that the manuscript may form part of the dissertation.

I declare that I have approved the above-mentioned manuscript and that my role in this study, as indicated above, is a representation of my actual contribution, and I hereby give my consent that it may be published as part of the MPharm study of *WE Agyakwa*.

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Prof MS Lubbe

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Dr JR Burger

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Dr NL Katende-Kyenda

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Ms M Cockeran

CHAPTER 1: INTRODUCTION

1.1 Introduction

This chapter focuses on the general overview of the study, centering on providing a background to the study, defining the problem, questions that will be answered, aims, specific objectives and methodology that will be utilised in the study. The chapter concludes with the division of chapters.

1.2 Background

In the 1920s, when Sir Alexander Fleming accidentally discovered penicillin, little did the world know that it will revolutionise the mystery behind “the germ theory of disease” (White, 2012:10). The identification of the causative organism of infections allowed for a much better understanding of their epidemiology, which, in turn, informed prevention strategies (Nelson & Williams, 2007:15). Antibiotics, a major pharmacological group, have been found to be of great benefit in plants and animals (Barbosa & Levy, 2000:303). This has permitted the indiscriminate use of antibiotics resulting in resistance over prolonged use.

There is a global interest to control antibiotic usage. This stems from the fact that infections cover a larger percentage of diseases that affect people; and South Africa is no exception. According to the World Health Organization (WHO, 2013), infectious diseases form 60% of the disease burden in the country, with 78% of lives being lost through limited access to available and affordable antimicrobials needed to treat infections. Antimicrobial resistance (AMR) is an important public health concern, because it has a medical, social and economic impact on a population (WHO, 2014:36).

According to the World Health Organization (2001:1), antibiotic use is the “main driver of resistance.” Iconic studies by Chen *et al.* (1999:234), Laxminayaran and Brown (2001:189), and Turnidge and Christansen (2005:548) confirm antibiotic use correlating with the emergence of resistance. For example, in a study by Goossens and his co-workers (2005:579-587), involving sixteen European countries from January 1997 to December 2002, they identified a strong correlation between *Streptococcus pneumonia* resistance and an increased use of the macrolide, erythromycin. Higher consumption of clarithromycin also correlated with the predominance of macrolide-resistant *Streptococcus pneumoniae*. Pakyz and his colleagues (2012:1-2) found, in their study from 2002 to 2009 in the United States, a direct correlation between fluoroquinolone-resistant *Pseudomonas aeruginosa* and fluoroquinolone use. A decrease in the use of fluoroquinolones in the hospitals under study showed a decrease in

fluoroquinolone-resistant *Pseudomonas aeruginosa.* Ciprofloxacin and levofloxacin were associated with a greater proportion of resistance.

In view of the assumption that an increased usage of antibiotics correlates with antimicrobial resistance, information concerning the consumption pattern of antibiotics is crucial to explore these dynamics (Mackenzie & Gould, 2005:105). Comprehensive data on the use of antibiotics are important for the analyses and interpretation of prescribing habits, the evaluation of compliance with clinical guidelines and linkage with antimicrobial resistance data. Countries are encouraged, among other measures, to monitor volumes and patterns of use of antibiotics and to evaluate the impact of control measures (WHO, 2001:1).

Analysing prescribing patterns validated with laboratory findings will assist in curbing emerging antibiotic resistance patterns. In South Africa, there is a great scope to provide quality management in the use of antibiotics. There is irrational use of antibiotics in both public and private sectors in the form of prescribing antibiotics for cases that do not require them, e.g. flu, prescribing for long durations, no de-escalation, and prescribing two or more antibiotics that are not suitable (Visser *et al*., 2011:587).

In November 2001, the European Centre for Disease Control (ECDC) formed the European Surveillance on Antibiotic Consumption (ESAC) project (ECDC, 2010:3). The aim of this project involves the monitoring of antibiotic consumption in all the European countries and determining the population's exposure to antibiotics. The data sources include national sales, reimbursement data and information from national drug registries. The number of DDDs (daily defined doses) per one thousand (1 000) inhabitants per day; and the DDD per number of packages per one thousand (1 000) inhabitants per day are the main indicators for reporting consumption. Their goal was to document variations in antibiotic consumption and to translate them into quality indicators for public health monitoring over a specified time and place. This will, in turn, aid in providing appropriate interventions when needed and to assess the effectiveness of previous programmes (ECDC, 2010:7).

A pilot antibiotic stewardship project was launched in the private healthcare sector of South Africa in 2009 (Winters & Gelband, 2011:556). The aim of this project was to foster the responsible use of antibiotics by raising awareness of prescribing issues (both misuse and appropriateness of use of antibiotics) to solve the problem of emerging resistance (Hanlon & Hodges, 2013:129-130). Antibiotic stewardship can help in reducing the platform of antibiotic resistance being addressed by the Global Antibiotic Resistance Partnership (GARP) in South Africa. The two main strategies for addressing resistance are to reduce the use in both humans and livestock by reducing the incidence of infections (Winters & Gelband, 2011:556).

Currently, South Africa is faced with levofloxacin-non-susceptible *Streptococcus pneumonia* in the treatment of multidrug resistant tuberculosis (MDR-TB) (von Gottberg *et al.*, 2008:1108), ciprofloxacin-resistant *Salmonella typhi* (Coovadia *et al*., 1992:91-100), and quinolone-resistant gonococci (Lewis, 2011:215-220). There is also a huge burden of sexually transmitted infections (STIs), which is a major cause of morbidity (Crowther-Gibson *et al.*, 2011:567). The introduction of checks and balances to monitor the use of fluoroquinolones in the treatment of these infections is crucial in limiting the problem of antibiotic resistance.

Fluoroquinolones are useful antimicrobials in South Africa. They are indicated for chronic bronchitis, community acquired pneumonia, sinusitis, complicated and uncomplicated urinary tract infections and soft tissue infections (Snyman, 2012:291). Currently, five of the nine fluoroquinolones that have been approved for human use are available in the South African market, *viz*. levofloxacin, ciprofloxacin, moxifloxacin, gemifloxacin and ofloxacin. These fluoroquinolones have good oral absorption and tissue penetration, relatively long elimination half-lives which permit once or twice daily dosing, a relatively low rate of serious adverse effects, and predictable drug-drug interactions (Jacoby & Hooper, 2012:119).

Factors influencing fluoroquinolone resistance include inadequate dosage, interactions reducing bioavailability, treatment of prosthetic infections and prolonged use in cystic fibrosis. Clinically significant drug-drug interactions involving fluoroquinolones include formation of chelates with metal ions such as aluminium, magnesium and calcium. These chelates reduce the gastro-intestinal absorption of the fluoroquinolones, and consequently reducing therapeutic activity (Scholar & Pratt, 2000:272). Xanthine derivatives (theophylline and caffeine) inhibit the metabolic pathway of fluoroquinolones; ciprofloxacin decreases the concentration of phenytoin, whereas ofloxacin and moxifloxacin enhance the effects of warfarin and its derivatives (Andriole, 2000:24). A combination of fluoroquinolones and non-steroidal anti-inflammatory drugs can cause synergistic inhibition of the gamma-aminobutyric acid (GABA) receptors in the central nervous system (Stahlmann & Lode, 1999:311). Nitrofurantoin is furthermore contra-indicated with ciprofloxacin use (Griffin & d'Arcy, 1997:388). Anderson *et al.* (2012:56) believe that fluoroquinolones still remain attractive antibiotics to preserve in this era despite their clinically significant drug interactions. Though the fluoroquinolones may not be the most prescribed antibiotics, monitoring their use over time will help in solving and preventing resistance, as said by Lord Kevin (1824-1907), "*If you can not measure it, you can not improve it.*"

We have approached an era where the pipeline has run dry for newer antibiotics. There is strong interest in preserving what we already have before we reach a 'nil-antibiotic era'. For South Africa, the answer is in strengthening the Antibiotic Stewardship project (Hans &

Ramsamy, 2013:368).

According to Frenk and De Ferranti (2012:862), “The paradox of health care is that it is one of the most powerful ways of fighting poverty, yet it can itself be an impoverishing factor for families when societies do not ensure effective coverage with financial protection for all”. Health economics has become relevant globally because every government’s objective is to increase the quality of health with appreciable cost. South Africa devotes considerable financial and other resources to the health sector far more than other middle-income countries (McIntyre & Doherty 2004:380). Healthcare in South Africa is divided into the public and private sector, financed by four major groups, *viz*. government, households, employers and donors; the government being the largest contributor. Households form the second largest source of funds where there is payment of contributions to medical aid schemes, private insurances and out-of-pocket payments. The private sector is the major consumer of healthcare spending. Approximately 50% of expenditure is by the private sector (McIntyre & Doherty, 2004:380).

Medical aid schemes cover a larger percentage of private health care in the country, with an estimated coverage of 20% of the population (CMS, 2013:228). According to the Council for Medical Schemes (2012:119), medications formed 16% and 15% of the total expenditure for healthcare provided in 2010 and 2011, respectively. This decrease in the total cost on medications has been credited to strategies implemented by the medical aid schemes through generic substitution, pre-authorisation processes and a managed care approach (Kahne, 2013). Based on a report by the Intercontinental Marketing Services (IMS) Health in 2010, for example, Targocid® (piperacillin/tazobactam), Meronem™ (meropenem) and Augmentin™ (amoxicillin/clavulanate) were the top three antibiotics having 9.2, 8.4 and 5.6% of the total market share (Essack *et al*., 2011:566). These antibiotics formed part of the top twenty drugs from 2010 to 2012. Branded fluoroquinolones such as Tavanic® (levofloxacin) and Ciprobay® (ciprofloxacin) formed 4.1 and 1.4%, respectively, of the total market share of antibiotics used in 2010; Tavanic® has seen a 5% growth in the market share from 2009 to 2010 (Essack *et al*., 2011:566).

1.3 Problem statement

One of the most challenging issues facing the health sector is the emerging resistance to antibiotics owing to improper prescribing and patient non-compliance. Fluoroquinolones have been used for some time now to treat MDR-TB (Department of Health, 2012a). Tuberculosis being a major health burden in South Africa, growing resistance to conventional treatment will have a negative medical, social and economic impact on the country (Crowther-Gibson *et al*., 2011:567). Resistance alone is costly to a country’s financial resources, because there is more

expenditure on newer drugs that are more costly compared to conventional treatments (CDC, 2013:11; ECDC, 2009:13; Engemann *et al*., 2003:586).

Medical aid schemes in South Africa are concerned about the increase in the cost of antibiotics. There was an estimated 23% increase in the average cost of treatment involving antibiotics between 2009 and 2010 (Kantor, 2011). The major challenge is that there are few publications addressing the prescribing patterns of antibiotics and especially fluoroquinolones in the private sector of South Africa.

The first step in solving emerging resistance is by monitoring the prescribing patterns of antibiotics, either retrospectively or prospectively. Monitoring the use of antibiotics helps to detect early signals of irrational use. Presently in South Africa, the only published information on antibiotic consumption in the public sector is based on government tender documents. Information from the private sector is available from IMS Health, relying on data from wholesalers and direct sales from manufacturers to pharmacies (Essack *et al*., 2011:564-565). There is, however, little information on antibiotic use in the private sector of South Africa using prescription data employing the defined daily dose (DDD) unit of measurement for analysing drug use (Truter *et al*., 1996:678). Additionally, a major setback in the use of the DDD is its inaptness to monitor paediatric drug use (Liem *et al*., 2010:1301; Natsch *et al.,* 1998:23). This research seeks to analyse antibiotic use with special emphasis on fluoroquinolones in the private sector.

The following research questions were developed to help address the aim of the study:

- What major pharmacological groups of antibiotics are used globally?
- What are the prescribing patterns and indications of fluoroquinolones in patients younger than 18 years?
- Which quantitative methods are employed in measuring antibiotic use in healthcare settings?
- What are the changes in antibiotic prescribing trends during the study period and their implications?
- What is the total DDD/1 000 inhabitants/day of fluoroquinolones in patients older than 18 years during the study period?
- Are the prescribed daily doses (PDDs) and recommended daily doses (RDDs) of fluoroquinolone use in patients younger than 18 years comparable?

1.4 Aim of study

The aim of the study can be described using the general research goal with specific objectives.

1.4.1 General research goal

The goal of this research project was to determine the prescribing patterns of antibiotics with an emphasis on fluoroquinolones in the private health sector in South Africa, analysing eight years' prescription data, obtained from a South African Pharmaceutical Benefit Management (PBM) company.

1.4.2 The specific research objectives

The research project was conducted in two phases, consisting of a literature review and an empirical investigation. The specific objectives for each of the phases follow in the subsequent paragraphs.

- **Literature review**

The objectives of the literature review were to:

- Conceptualise antibiotics and their use.
- Determine, from literature, fluoroquinolones as a pharmacological group of antibiotics, their indications for use, side effects, drug-drug interactions and special precautions.
- Determine antibiotic prescribing patterns in Europe, the United States and Africa with an emphasis on fluoroquinolones; as well as resistance patterns in Africa.
- Identify interventions set up to monitor and control the use of antibiotics globally.

- **Empirical study**

The empirical study was aimed at:

- Investigating the prescribing patterns *viz*. age, gender, seasonal and geographic variations over the eight-year period for the various pharmacological groups of antibiotics.
- Describing the prescribing patterns of the various groups of fluoroquinolones in children *viz*. age, gender and speciality of prescribers over the study period; comparing the PDD to the RDD.
- Investigating specifically the prescribing patterns of the various groups of fluoroquinolones focusing on longitudinal prevalence variations using the defined daily dose (DDD) per 1 000 inhabitants per day for adults.

1.5 Method of research

To help address the main objectives of the study mentioned above, the study was based on two

main phases, focusing on the literature review and the empirical investigation.

1.5.1 Literature review

The Dictionary of Media and Communication (2014) defines a literature review as "*a formal, reflective survey of the most significant and relevant works of published and peer reviewed academic research on a particular topic, summarising and discussing their findings and methodologies in order to reflect the current state of knowledge in the field and key questions raised*". Aveyard (2010:5) and Hart (2003:13) further explain that the importance of doing a literature review is to provide more insight into the research topic and to allow the researcher to make a critical analysis of the literature available to draw impartial conclusions. The study reviewed books and published work from reliable sources, such as GoogleScholar, EBSCOhost, ScienceDirect, and Scopus to be able to address the main objectives outlined. Table 1.1 provides the section in which the above-mentioned objectives of the literature review were answered.

Table 1.1 Objectives outlined from literature review and sections in which they are addressed

Objective	Paragraph or section that addresses the objective
To conceptualise antibiotics and their use.	Refer to 2.1.1 to 2.1.2.12
To determine, from literature, fluoroquinolones as a pharmacological group of antibiotics, their indications for use, side effects, drug interactions and special precautions.	Refer to 2.1.2.13 to 2.1.2.13.8
To determine antibiotics' prescribing patterns in Europe, the United States and Africa with an emphasis on the fluoroquinolones; and resistance in Africa.	Refer to 2.3
To identify interventions set up to monitor and control the use of antibiotics globally.	Refer to 2.4

1.5.2 Empirical investigation

The subsequent paragraphs focus on the study design, source of data, study population, variables used and the method of analysing the data.

1.5.2.1 Study design

The study followed a quantitative, descriptive, observational design using retrospective, longitudinal medicine claims data provided by a nationally representative Pharmaceutical Benefit Management company (PBM). **Observational studies** are beneficial when variables in

the study can be identified and measured, excluding human interventions (Waning & Montagne, 2005:45). It also helps to provide information about the problems with drug use by variables such as person, time and place. The study follows a **descriptive** nature to provide insight into the trends in antibiotic use in the population. The study is also considered **retrospective** as data were collected between 2005 and 2012. According to Motheral *et al*. (2003:90), retrospective databases are useful in health-related studies because they provide large sample sizes and long observation times. Additionally, they are relatively cheaper to obtain and are expedient for time (Motheral *et al*., 2003:91).

1.5.2.2 Data source

Secondary data for the study were obtained from an administrative claims database of a South African Pharmaceutical Benefit Management (PBM) company. The PBM company (name withheld for confidentiality) has been in existence for twenty-four years providing services to thirty-six medical schemes in South Africa. The company also processes approximately 300 000 real-time and 30 000 doctors' transactions daily. Administrative claims databases are reliable sources of data because there is the avoidance of recall bias as they do not rely on patients' recall or interviews to obtain data. Data for the eight-year period were obtained from 1 January 2005 to 31 December 2012.

1.5.2.2.1 Validity and reliability of data

A vital aspect of good research is the validity and reliability of the data used. These are important to help produce accurate results and interpretations. Waning and Montagne (2005:123) define the validity of a measure as the degree to which the measure actually measures what it is designed to measure. Reliability is the degree of stability exhibited when a measurement is repeated under identical conditions (Waning & Montagne, 2005:123).

The PBM from which data were obtained for the study ensures the reliability and validity of data through gate-keeping services, eligibility services, utilisation management services, clinical management services and pricing management along with real-time benefit management. These validation processes ensure that claiming standards are met; for example, in the case of a missing or invalid product or member number, such a claim would be rejected. The PBM also conducts supplementary services such as integrated pre-authorisation services, prescribed minimum benefits (PMBs) and other conditions, and medicine management in capitation environments. All unpaid claims were excluded from the data as part of a cleaning-up process. The datasets were verified after each cleaning process by performing random data checks. Park and Stergachis (2008:519) describe claims databases as multipurpose because they

provide administrative records and health service files. These databases must be of high quality; information on individuals should be linkable across datasets; and patients in the datasets must be traceable to provide longitudinal follow-up (Park & Stergachis, 2008:519). Table 1.2 is a summary of measures to validate data used by the PBM.

Table 1.2 Claim processing checks to ensure validity of data by PBM

Data integrity validation process	Example
Eligibility management	Claim field format checks Provider validation checks Member validation checks Verification of dependent codes Checks for waiting period Duplicate check
Medicine utilisation management	Verification of refill limits and fill limitations per period Product quantity limits Pre-authorisation for products that require them Patients specific exclusions Drug to age range limitations Drug to gender limitations Invalid prescriber speciality Broad category exclusions Specific products excluded Waiting periods
Clinical management	Ingredients duplication and maximum daily dose exceeded Therapeutic duplication Drug-drug interaction Drug-allergy interactions Drug-age interactions Drug-gender interactions Drug-disease interactions Drug-inferred health state interactions
Pricing management	Continuous price file management Application of reference pricing
Formulary management	Management of chronic disease list prescribed minimum benefits and non-chronic disease list conditions Daily real-time benefit validation
Real-time benefit validation	Real-time member validation and approval of claims

1.5.2.3 Study population

This section consists of the criteria utilised in the selection of the study population. The process followed in extracting data for the study population is illustrated in Figure 1.1.

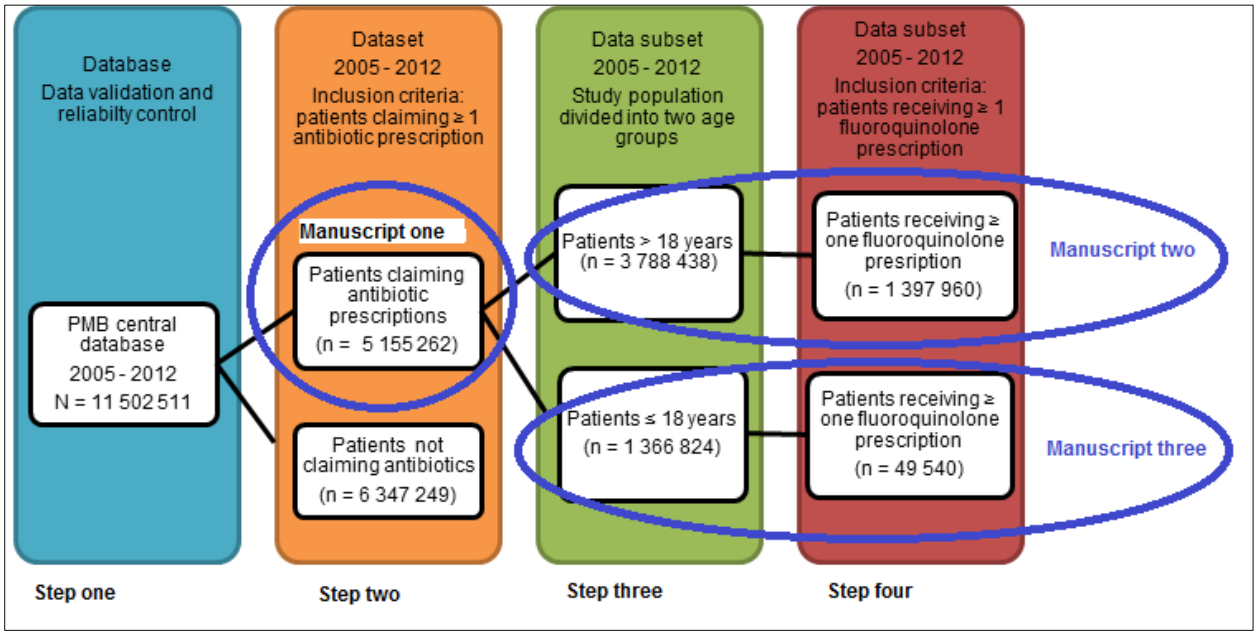

Figure 1.1 Selection procedures for study population

The following steps were employed in selecting the target population for the study:

Step 1: Retrieving data from the PBM central database

The elements selected from the PBM's central database are shown in Table 1.3. An additional field representing the Monthly Index of Medical Specialties (MIMS®) classification code was included for each active ingredient that formed part of the dataset. The MIMS classification code for antimicrobials is 18 and the sub codes 18.1 to 18.7 were selected from 1 January 2005 to 31 December 2012. Antibiotics analysed included the penicillins, cephalosporins, carbapenems, macrolides, aminoglycosides, chloramphenicol, quinolones and tetracyclines. Data for 11 502 511 patients were obtained from the central PBM. The female-to-male ratio was 1.2:1.

Table 1.3 Selected data elements in the PBM used in the study

Type of data	Selected database element
Membership	Date of birth (to determine the age of the patient) Gender Anonymous membership identifier Anonymous member dependent identifier
Medicine claims	Anonymous prescriber type identifier Anonymous provider identifier National Pharmaceutical Product Interface (NAPPI®) code Drug trade name Quantity dispensed Day's supply Date filled

Step 2: Applying inclusion criteria to obtain data subset for patients claiming ≥ one antibiotic prescription

A total of 5 155 262 patients claiming one or more antibiotic prescriptions were extracted from the database by applying the inclusion criteria (refer to Fig. 1.1). This formed 44.8% of the total population (N = 11 502 511). The female-to-male ratio was 1.2:1.

Step 3: Study population was divided into two age groups (patients older than 18 years and patients 18 years and younger claiming ≥ one antibiotic prescription)

The data subset was divided into main age groups: patients 18 years and younger and patients older than 18 years who claimed antibiotic prescriptions over the study period.

A total of 3 788 438 patients older than 18 years were extracted from the dataset. They represented 73.5% of the total number of patients who claimed antibiotic prescriptions during the study period (n = 5 155 262).

A total of 1 366 824 patients 18 years and younger were extracted from the dataset. This study population represented 26.5% of the total number of patients who claimed antibiotic prescriptions during the study period (n = 5 155 262).

Step 4: Applying inclusion criteria to obtain data subset for patients claiming ≥ one fluoroquinolone prescription in the two age groups

The data subset obtained from step 3 was further narrowed down applying the inclusion criteria

(refer to Fig. 1.1).

A total of 1 397 960 patients older than 18 years who claimed at least one fluoroquinolone prescription during the study period were extracted from the dataset. This represented 37.0% of the total number of patients older than 18 years who claimed at least one antibiotic prescription (n = 3 788 438) and 27.1% of the total number of patients who claimed antibiotic prescriptions (n = 5 155 262). The female-to-male ratio was 1.3:1.

A total of 49 540 patients 18 years and younger who claimed at least one fluoroquinolone prescription during the study period were extracted from the dataset. This represented 3.6% of the total number of patients 18 years and younger who claimed at least one antibiotic prescription (n = 1 366 824) and 1% of the total number of patients who claimed antibiotic prescriptions (n = 5 155 262). The female-to-male ratio was 1.2:1.

1.5.2.4 Study variables

A variable is described as a measurable characteristic relating to an individual or a group (Oxford Concise Medical Dictionary, 2014). The subsequent sections focus on the various independent and dependent variables employed in this study.

1.5.2.4.1 Independent variables

An independent variable is a characteristic being observed or measured and is hypothesised to influence an event or outcome (CDC, 2012:20). Heiman (2014:24) further explains independent variables as those manipulated by the investigator to produce an outcome of interest. The independent variables analysed in the study were age, gender, geography, seasons and specialty of prescriber. These variables were chosen to provide more insight into the trends in antibiotic use over time. The following paragraphs describe the independent variables used in the study.

- **Age**

Age is an important characteristic of a population because most health-related concerns vary with this variable (CDC, 2012:24). The ages of patients in the study were calculated by using the age of the patient at the time of treatment with respect to their date of birth using 1 January of the following year as reference. It is recommended that age groups be narrow enough to detect any age-related patterns that may be present in the data. The age of the adult study populations was stratified according to the following groups illustrated below:

Group 1 - 18<n≤ 30 years
Group 2 - 30<n ≤ 45years
Group 3 - 45<n≤ 65 years
Group 4 - above 65 years

The age group for the paediatric study population is also outlined as follows:
Group 1 - 0 ≤ n ≤ 5 years
Group 2 - 5 < n ≤12 years
Group 3 - 12 < n ≤18 years

- **Gender**

Antibiotic use varies with respect to gender. Most studies evaluating antibiotic use in a given population have observed a higher use in males compared to females (Abula & Kedir, 2004:36; Amadeo *et al*., 2010:2248; Raveh *et al*., 2001:143; Stuart *et al*., 2012:1146). In the study, gender was defined as patients being either male or female.

- **Geography**

The Statistical Analysis System®, SAS 9.3® (SAS Institute Inc., 2012) programme was used to group all prescriber practice addresses according to the postal codes indicated for every prescriber's practice to categorise them according to the nine provinces.

- **Prescribers**

A prescriber is defined by the Oxford English Dictionary (2013) as a person who writes or authorises a medical prescription. The prescribers were divided into the following categories:

- General medical practitioners: This group includes all the medical providers who are registered with the Health Professions Council of South Africa (HPCSA) as a general medical practitioner.
- Paediatricians.
- Pharmacotherapists: This group includes all qualified personnel who are registered with the South African Pharmacy Council.
- Specialists: cardiologists, neurologists, obstetricians and gynaecologists, urologists and oncologists.
- Other: This group includes prescribers such as dentists and dermatologists.

- **Seasons**

The use of antibiotics has been found to change seasonally, with the most use occurring during the winter months (Adrianssens *et al*., 2011a:S6-S7; Polk *et al*., 2004:499). The Centre for Disease Control (2012:34) recommends the use of more than a year's data to draw reasonable conclusions of seasonal patterns of drug use (CDC, 2012:34). This study therefore employed eight years' data and is consequently valuable to explore seasonal trends. In this study, the year was divided into three seasons, consisting of four months, marking each season, as illustrated below:

Season 1 - January-April
Season 2 - May-August
Season 3 - September-December

1.5.2.4.2 Dependent variables

Dependent variables are described as outcome variables that are influenced by the independent variables. The dependent variables from the study included the following:

- The average number of prescriptions per patient per year.
- The average number of antibiotic agents per prescription per patient.
- The major pharmacological groups of antibiotics prescribed per year.
- The different antibiotic agents prescribed per year.
- The defined daily doses (DDD)/1 000 inhabitants/day of fluoroquinolone use in adults.
- The average DDD per prescription per patient per year in adults.
- Comparison of the prescribed daily dose (PDD) and the recommended daily dose (RDD) of fluoroquinolones in children was also analysed.

The following prescription-related measurements were done to help describe antibiotic use during the study:

- **Prescription volume**

A prescription is defined by the Oxford Online Dictionary (2013) as "*an instruction written by a medical practitioner that authorises a patient to be issued with a medicine or treatment"*. Medicine is defined by the Medicines and Related Substances Amendment Act (Act 72 of 2008) as *"any substance or mixture of substances used or purporting to be suitable for use or manufactured or sold for use in the diagnoses, treatment, mitigation, modification, or prevention of disease, abnormal physical or mental state or the symptoms thereof in humans; or restoring,*

correcting or modifying any somatic or psychotic or organic function in humans, and include any veterinary medicine" (Department of Health, 2009).

The number of prescriptions and medicine items claimed by beneficiaries was used to describe the prescribing volume. Patients claiming at least one antibiotic using the MIMS® classification (Sections 18.1 to 18.7) during the study period (January 1, 2005 to December 31, 2012) were evaluated.

- **Defined daily doses (DDD), prescribed daily doses (PDD) and the recommended daily doses (RDD)**

The defined daily dose (DDD) is *the assumed average maintenance dose per day for a drug used for its main indication in adults* (WHO, 2003:20). The DDD is a unit of measurement and it is not a reflection of the prescribed daily dose. The DDD per 1 000 inhabitants per day provides a rough estimate of the study population that are treated daily with a particular drug (WHO, 2013:26). This was calculated by determining the total amount of the drug dispensed (in milligrams), divided by the DDD conversion factor and the population (using the total number of beneficiaries covered by medical aid schemes registered under the PBM company during the study period, as denominator for each respective year) to obtain the results in DDD-inhabitants/year. The DDD/inhabitants/year was then divided by 365 days and multiplied by 1 000, to obtain the results in DDD/1000 inhabitants/day.

The prescribed daily dose (PDD) can be defined as *the average dose prescribed according to a representative sample of prescriptions* (WHO, 2003:20). The PDDs were calculated from the dataset by multiplying the quantity prescribed by the strength or the concentration per unit in milligrams divided by the days' supplied.

The maximum recommended daily dose for each fluoroquinolone, shown in Table 1.4, was obtained by cross-referencing from the literature.

Table 1.4 Maximum recommended daily doses of fluoroquinolones in patients 18 years and below

Fluoroquinolone	Route of administration	Dose (mg/kg)	Maximum daily dose (mg)	References
Ciprofloxacin	oral	15 – 20	1 500	BNF for children (2012); Rossiter (2012); Department of Health (2013); Sweetman (2012); Takemoto *et al*. (2010); WHO (2005)
	intravenous	10 – 15	1 200	
Ofloxacin	oral	7.5 – 15	800	WHO (2008)
Levofloxacin	oral	7.5 – 10	750	WHO (2008)
		15 – 20	1 000	Department of Health (2013)
Moxifloxacin	oral/ intravenous	7.5 – 10	400	Department of Health (2013); WHO (2008)
Gatifloxacin	oral	10	400	Sweetman (2012)
Norfloxacin		-	800	Sweetman (2012)
Enoxacin	oral	-	800	Sweetman (2012)
Gemifloxacin	oral	-	320	Sweetman (2012)
Lomefloxacin	oral	-	400	Sweetman (2012)

1.5.2.5 Statistical analyses

The data were analysed by using Statistical Analysis System®, SAS 9.3® (SAS Institute Inc., 2012). The afore-mentioned study variables (refer to section 1.5.2.4) were analysed using both descriptive and inferential statistics. The paragraphs below provide a brief summary of the test statistics employed to address the objectives of the empirical investigation.

1.5.2.5.1 Descriptive statistics

Heiman (2014:21) explains descriptive statistics as ways of organising and summarising sample data to facilitate effective communication and describe their important characteristics. Descriptive statistics also aid in predicting future outcomes in a population. The subsequent paragraphs provide a brief summary of the various descriptive statistics utilised in the study.

- **Frequency and prevalence**

The Oxford Online Dictionary (2013) defines the term frequency as "*the rate at which something occurs over a particular period of time or in a given sample*". Prevalence is the number of existing cases at a point in time in a population size defined by specific characteristics (Waning

& Montagne, 2005:20). Prevalence is the probability of the occurrence of a condition and is obtained by dividing the number of cases in the population by the total number in the population. For the purpose of this study, the numerators consisted of patients receiving one or more antibiotics and the denominator was the total number of patients in the database stratified according to age and gender.

- **Median**

The median is defined as "*the middle observation if the sample size is odd and the average of the two middle observations if the sample size is even, arranged in rank order*" (Hettmansperger, 2005:3103). The median of a distribution is the point that divides the sample into two equal parts.

- **Average or mean**

The mean is defined as "*the central point or tendency of a set of numerical data*" (Smith, 2005:3063). It is derived from the summation of the set of numerical observations divided by the number of observation. Mathematically, average or mean is denoted by $\bar{x}$ for a dataset represented by x_1, x_2, x_3...x_n,

$$\bar{x} = (x_1 + x_2 + x_3 + x_n,)/n$$

Where $\bar{x}$ is the average

x_n is the individual values and

n is the sample size.

- **Minimum and maximum**

Minimum is defined by the Oxford Online Dictionary (2014) as "*the smallest value which a variable takes"*. Maximum is "*the highest value a variable takes"* (Oxford Online dictionary, 2014).

- **Range**

The range is a type of descriptive statistic that crudely measures the distance between the two most extreme scores in a distribution. It is given by:

Range = Highest score – Lowest score

The range roughly describes the spread of a distribution as it involves the least typical and most frequent scores (Heiman, 2014:87).

- **Standard deviation**

The standard deviation (SD) is an effective means of describing how data from a result differ from each other (Heiman, 2014:86). It is defined as the positive square root of the variance, where the variance of a group of data is a means of providing useful information on how the individual data differ around the mean and how spread out a distribution is (Waning & Montagne, 2005:85). The larger the standard deviation, the more variability there is in the sample. The opposite is also true; the smaller the variability, the greater the consistency between the results obtained. The standard deviation also describes how the mean accurately describes the distribution of the data (Heiman, 2014:86). The standard deviation is given as follows:

$$SD = \sqrt{\frac{\sum(x_1 - \bar{x})^2}{n-1}}$$

where SD is the standard deviation

x_1 is the individual value

$\bar{x}$ is the mean

n is the sample size

- **Standard error (SE)**

The standard error provides useful information about the certainty of the mean. Similar to the standard deviation, the larger the standard error, the more uncertain the standard mean. The standard error of the mean is given by:

$$SE = \sqrt{\frac{S^2}{N}}$$

Where SE is the standard error

S^2 is the variance

N is the sample size

- **Confidence interval (CI)**

The confidence interval (CI) is a range of values that contain a parameter of interest from a

sample population with a certain degree of certainty (Waning & Montagne, 2005:88). In this study, the 95% CI was used. Mathematically, the 95% CI is calculated as follows:

$$95\%\ CI = \mu \pm (2 \times SE)$$

Where μ is the mean of the sample population

SE is the standard error of the mean.

The 95% CI simply means that an investigator is 95% certain that an estimate from the population of interest falls between a range of values, also known as the confidence interval. Additionally, the confidence interval is a means of indicating the statistical significance of results obtained from a study (Waning & Montagne, 2005:88).

1.5.2.5.2 Inferential statistics

Inferential statistics are procedures performed to test hypotheses in a study and to determine whether there are significant differences in association in order to minimise sampling errors (Asadoorian & Kantarelis, 2005:2; Heiman, 2014:22; Waning & Montage, 2005:91). According to Cohen (1988:4), the power of statistical tests is highly dependent on the criteria for significance, the reliability of the sample results and the measure of the effect size.

- **Statistical significance**

An acceptable level of chance occurrence (alpha, α), also referred to as the level of significance (*p*-value), was determined before the collection of data to control type I error. The *p*-value is defined as the probability of obtaining an outcome that is at least as extreme as the one that is actually observed provided that the hypothesis is correct (Anders, 1993:36). It shows how consistent the observed outcome is hypothesised. In this study, a *p*-value of 0.05 was used. Observations with *p*-values less than or equal to 0.05 were considered to be statistically significant and *vice versa*. The *p*-value is, however, sensitive to the size of the study population and the magnitude of the differences observed between two groups (Waning & Montagne, 2005:92). Smaller *p*-values are easily obtained in large sample sizes, which may not be necessarily practical in reality. Additionally, small differences observed between groups in large study populations will be statistically significant and *vice versa* (Anders, 1993:41). The *p*-values, however, do not give the strength of association between two groups and therefore the use of effect size measures (Anders, 1993:41).

- **Statistical tests**

The following tests were used to determine the statistical significance of the various study variables and outcomes derived from the study:

a) The two-sample *t*-test

This is a test used to determine the statistical significance of the means of two independent groups (Heiman, 2014:264). In this study, the *t*-test was used to determine the statistical significance in antibiotic prescribing between males and females. The Statistical Analysis System®, SAS 9.3® (SAS Institute Inc., 2012) was used in computing the *t*-test.

b) Analysis of variance (ANOVA)

The ANOVA is used to compare the variances between groups and that within groups (Carr, 2012:157). The test gives a test statistic known as the F-ratio, which gives a level of statistical significance (i.e. the *p*-value) (Carr, 2012:157). In this study, the ANOVA was used to determine the level of significance between antibiotic prescribing and the different age groups, provinces and seasons. The Statistical Analysis System®, SAS 9.3® (SAS Institute Inc., 2012) was used in computing ANOVA in this study.

c) Chi-square test (χ^2)

The chi-square test is a means of determining the level of significance between two or more groups of categorical data, displaying data by means of contingency tables (Heiman, 2014:252). The chi-square statistic is determined from the observed and expected counts from the contingency tables (Heiman, 2014:252). In this study, the chi-square test was used to determine the level of significance between antibiotic prescribing and the different age groups by using the Statistical Analysis System®, SAS 9.3® (SAS Institute Inc., 2012).

- **Effect size**

Effect size is the degree to which a phenomenon exists (Cohen, 1988:4). Statistical significance is most likely to occur in large sample sizes, though with very small effect sizes (Anders, 1993:41). In this study, the Cohen's *d*-value and Cramer's *V* were used to determine the effect sizes of statistically significant results. The following paragraphs provide a brief summary on the aforementioned effect size measures:

a) Cohen's *d*-value

Cohen's *d*-value is used to determine the effect size in a sample population when applying the *t*-test (Cohen, 1988:24). It is the absolute difference between two population means divided by the common standard deviation. Mathematically, it is given by:

$$d = \left| \frac{\overline{X_A} - \overline{X_B}}{\sigma} \right|$$

Where *d* is the effect size index

$\overline{X_B}$ and $\overline{X_B}$ are the means of the two populations

σ is the standard deviation of either population (since they are assumed to be equal) (Cohen, 1988:24).

According to Cohen (1988:29), the measure of the effect size is categorised as follows:

- Small effect size, *d* = 0.2
- Medium effect size, *d* = 0.5
- Large effect size, *d* = 0.8.

A *d*-value ≥ 0.8 was considered practically significant.

b) Cramer's *V*

It is a measure of association used to adjust the chi-square statistic for the difference in sample size and the dimensions of the contingency tables (Heiman, 2011:352). It is the most suitable measure of association for tables with more than two rows and columns (Healey, 2013:293). Mathematically, the Cramer's *V* is given by:

$$V = \sqrt{\frac{x^2}{nt}}$$

Where *V* is the Cramer's *V* value

x^2 is the chi-square statistic,

n is the sample size, and

t is the minimum of the number of rows minus one or the number of column minus 1.

The value of the Cramer's *V* is interpreted as follows (Rea & Parker, 2005:189):

- negligible association, *V* is > 0.0, ≤ 0.1;
- weak association, *V* is > 0.1, ≤ 0.2;
- moderate, *V* is > 0.2, ≤ 0.4;
- relatively strong association, *V* is > 0.4, ≤ 0.6;

- strong association, *V* is > 0.6, ≤ 0.8;
- very strong association, *V* is > 0.8 to 1.0.

A Cramer's *V* value ≥ 0.5 was considered to be practically significant.

1.5.3 Measures to ensure validity of the study

The use of databases for pharmacoepidemiological research has several advantages, such as large sample sizes, limitation of biases (recall and reporting), lower costs in data acquisition and shorter timeframe in data collection (Hall *et al*., 2012:1; Strom, 2006:188). Although the uses of databases are advantageous, there are factors that limit their use. These factors include the uncertainty of the validity of diagnoses; lack of information with regard to confounding; incomplete data due to medications obtained without prescriptions or not included in the patients' health benefit plan (Strom, 2006:188). Additionally, the population in the database are unstable due to patients' changes in health plan and cancellation of plan.

To address these flaws, guidelines for good pharmacoepidemiological research from automated databases have been enacted. In Table 1.4, a checklist to conduct studies utilising retrospective databases has been provided to ensure the robustness of the study, adapted from Motheral *et al*. (2003:90-97) and Hall *et al*. (2012:2-9), and The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (2013:4-42).

Table 1.5 Checklist for conducting retrospective database research

Aspect		Description	Answer	Section that addresses the aspect
Data source				
Database selection	**Relevance**	Have the data attributes been described in sufficient detail for decision-makers to determine there was a good rationale for using the data source, the data source's overall generalisability, and how the findings can be interpreted within the context of their own organisation?	Yes	Paragraphs 1.5.2.2 and 1.5.4
	Population covered	Does the resource include an appropriate population in terms of size, coverage and representativeness?	Yes	Paragraph 1.5.2.3
	Capture of study variables	Are all exposures, outcomes and other study variables captured in sufficient detail without bias and accessible for research?	Yes	Paragraph 1.5.2.4
	Continuous and consistent data capture	Are there any breaks or changes in data collection over time for either individual patient or the whole population during the study observation period? Are there any inconsistencies in provision of healthcare or capture of study variables across the database population?	Not applicable	
	Record duration and data latency	Is the average patient record duration, as well as the time between the occurrence of the exposure and data collection, sufficiently long for the study event?	Not applicable	
	Database expertise	Is the expertise required to use the resource available in-house or else-where?	Not applicable	
Use of multiple resources	**Multiple resources linked to increase breadth of patient information**	Can data resources be linked	Yes	Paragraphs 1.5.2.2 and 1.5.4

Table 1.5 Checklist for conducting retrospective database studies (continued)

Aspect		Description	Answer	Section that addresses the aspect
Data source				
Use of multiple resources	**Multiple resources linked to increase numbers**	Are the data sources and data systems compatible in metrics, policy and terminology?	Not applicable	
	Data storage and analysis	In multi-institutional studies, should a central or distributed system be used?	Not applicable	
Extraction and analysis of the study population	**Specification of extraction**	Are the following specified in detail: how to extract the study population and variables, code lists and non-coded systems, retrieval and merging additional external data, output and final analysis?	Yes	Paragraphs 1.5.2.3.1 and 1.5.2.3.1
Privacy and security	**Compliance with privacy and security policy**	Have all relevant local, regional and national policies been complied with?	Yes	Paragraph 1.6
	Limited use of identifying information	Are all direct identifiers removed or masked? Whose responsibility is it to ensure privacy?	Yes	
	Secure data storage and transfer	Is there a formal data security policy, and has it been adhered to?	Yes	Paragraph 1.6
	Review of policy and procedures	Are regular policy reviews adhered to? Has the use of new database, collection of additional patient or physician data, use of multiple resources, or narrative data impacted confidentiality?	Not applicable	
Quality and validation process	**Overall database**	Have appropriate general quality checks been completed?	Yes	Paragraph 1.5.2.2.1
	Study population	Has the annotated programming code been reviewed by an independent programmer?	Yes	

Table 1.5 Checklist for conducting retrospective database studies (continued)

Aspect		Description	Answer	Section that addresses the aspect
Data source				
Documentation	**Format**	Are rules of Guidelines for Good Pharmacoepidemiology practices followed, including storage and indexing?	Yes	Paragraph 1.5.3
	Reliability and validity	Have the reliability and validity of the data been described, including any data quality checks and data cleaning procedures?	Yes	Paragraph 1.5.4
Research methodology				
Methods	**Data analysis plan**	Was a data analysis plan, including study hypotheses, developed *a priori?*	Not applicable	
	Design selection	Has the investigator provided a rationale for the particular research design?	Yes	The rationale for the study design is explained in paragraph 1.5.2.1
	Research design limitations	Did the author identify and address potential limitations of the design?	Yes	Paragraph 4.4
	Treatment effect	For studies that are trying to make inferences about the effects of an intervention, does the study include a comparison group and have the authors described the process of identifying the comparison group and the characteristics of the comparison group as they relate to the intervention group?	Not applicable	

Table 1.5 Checklist for conducting retrospective database studies (continued)

Aspect		Description	Answer	Section that addresses the aspect
Study population and variable definitions	**Sample selection**	Have the inclusion and exclusion criteria and the steps used to derive the final sample from the initial population been described?	Yes	The study population was selected based on criteria explained in paragraphs 1.5.2.3.1 and 1.5.2.3.2
	Eligibility	Are subjects eligible for the time period over which measurement is occurring?	Yes	The study covers an eight-year period following a descriptive nature, refer to paragraph 1.5.2.1
	Censoring	Were inclusion/exclusion or eligibility criteria used to address censoring and was the impact on study findings discussed?	Not applicable	
	Operational definitions	Are case (subjects) and end point (outcomes) criteria explicitly defined using diagnoses, drug markers, procedure codes, and/or other criteria?	Yes	Patients claiming one or more antibiotics were used, with the term antibiotics referring to the MIMS® classification 18. 1 to 18.7; refer to paragraph 1.5.2.3.1.
	Timing of outcome	Is there a clear temporal (sequential) relationship between the exposure and outcome?	Not applicable	
	Event capture	Are the data, as collected, able to identify the intervention and outcomes if they actually occurred?	Not applicable	
	Disease history	Is there a link between the natural history of the disease being studied and the time period for analysis?	Not applicable	
	Resource valuation	For the studies that examine costs, have the authors defined and measured an exhaustive list of resources affected by the intervention given the perspective of the study and have resource prices been adjusted to yield a consistent valuation that reflects the opportunity cost of the resource?	Not applicable	

Table 1.5 Checklist for conducting retrospective database studies (continued)

Aspect		Description	Answer	Section that addresses the aspect
Statistics	**Control variables**	If the goal of the study is to examine treatment effects, what methods have been used to control for other variables that may affect the outcome of interest?	Not applicable	
	Statistical model	Have the authors explained the rationale for the model/statistical method used?	Yes	Refer to paragraph 1.5.3.
	Influential cases	Have the authors examined the sensitivity of the results to influential cases?	Not applicable	
	Relevant variables	Have the authors identified all variables hypothesised to influence the outcome of interest and included all available variables in their model?	Yes	Refer to paragraph 1.5.2.4.
	Testing statistical assumptions	Do the authors investigate the validity of the statistical assumptions underlying their analysis?	Not applicable	
	Multiple tests	If analyses of multiple groups are carried out, are the statistical tests adjusted to reflect this?	Not applicable	
	Model prediction	If the authors utilise multivariate statistical techniques in their analysis, do they discuss how well the model predicts what it is intended to predict?	Not applicable	
Discussion and conclusion	**Theoretical basis**	Have the authors provided a theory for the findings and have they ruled out other plausible alternative explanations for the finding?	Yes	Refer to Chapter 3
	Practical versus statistical significance	Have the statistical findings been interpreted in terms of their clinical or economical relevance?	Yes	Refer to Chapter 3
	Generalizability	Have the discussed covered the populations and settings to which the results can be generalised?	Yes	Refer to Chapter 3

1.6 Ethical aspect of research

Permission to conduct the study was obtained from the board of directors of the PBM, as well as the Ethics Committee of the North-West University (NWU-0046-08-550). Data privacy and confidentiality were maintained at all times; therefore, no patient or medical scheme/administrator could be traced. Additionally, it was not possible to determine which prescribers or providers (i.e. name of the prescriber/provider) were involved in the prescribing/dispensing of the medicine items. The PBM providing the data for the study is furthermore nowhere identified in this study. The researcher, study promoter and co-promoter furthermore signed confidentiality agreements.

The research was not sponsored by the private pharmaceutical sector or the PBM providing the data, minimising the potential for any bias in the study. All views expressed in this study are those of the researcher and do not necessarily reflect the official policy or position of the institution.

1.7 Chapter division

The study is presented in an article format. Chapter 1 describes the background to the study, problem, aim of the research and research methodology. Chapter 2 provides a comprehensive literature review of prescribing patterns of antibiotics and relevant topics to provide more insight into the topic being analysed. Chapter 3 consists of manuscripts submitted to the proposed journals involving the method of research, results and discussions. Chapter 4 provides detailed discussions of the main findings, comparing these findings to relevant literature, limitations and strengths of the study, as well as an elaborate list of recommendations for future studies.

1.8 Chapter summary

In this chapter, it has been established that the use of antibiotics has been linked with the emergence of resistance. However, there is little published data on the consumption of antibiotics in many countries. The main aim and method of research were also established. The next chapter focuses on antibiotics, summarising the main sub-pharmacological groups; antimicrobial resistance; patterns of antibiotic usage globally; and quantitative methods of measuring antibiotic use.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

This chapter focuses on providing a general summary of antibiotics and their use; determining, from the literature, fluoroquinolones as a pharmacological group of antibiotics, their indications, side effects, drug interactions and special precautions; determining resistance patterns in Africa; antibiotics prescribing in Europe, the United States and South Africa, with an emphasis on fluoroquinolones; and identifying interventions set up to monitor and control the use of antibiotics in Europe, the United States, Africa and South Africa.

2.2 Antimicrobial agents

Antimicrobials are defined as low molecular microbial metabolites that limit the growth of micro-organisms at low concentrations (Gelone & O'Donnell, 2005:1633; Lancini *et al*., 1995:1). Chambers (2001a:1143) goes further to define antimicrobials as substances produced by various species of micro-organisms that suppress the growth of other organisms. The term, 'antimicrobials', has also been used to refer to synthetic antimicrobial agents. Although antimicrobial agents were discovered long ago, the beginning of modern chemotherapy started with the discovery of penicillin (Garrold, 1964:1).

2.2.1 Classification of antimicrobial agents

Antimicrobial agents can be classified according to their mechanism of action and chemical structure (Chambers, 2001a:1143; Gelone & O'Donnell, 2005:1633). Five bacterial targets have been exploited in the development of antimicrobial drugs (Hooper, 2001:32; Sefton, 2002:558), which include cell wall synthesis, protein synthesis, ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) syntheses, as well as intermediary metabolism in the bacteria cell. Table 2.1 illustrates the mechanism of action of the various antibacterial agents and examples for each (adapted from Sefton, 2002:558; Chambers, 2001a:1144).

Table 2.1 Mechanism of action of pharmacological groups of antimicrobials

Mechanism of action	Antimicrobial agents
Agents that inhibit synthesis of bacterial cell wall.	Penicillin, cephalosporin and carbapenems
Agents that act directly on the cell membrane affecting permeability resulting in leakage of intracellular components.	Polymyxin
Agents that affect the functions of the 30S and 50S ribosomal subunits causing reversible inhibition of protein synthesis.	Chloramphenicol, tetracycline, macrolides
Agents that irreversibly bind to 30S subunits of the ribosomes altering protein subunits.	Aminoglycosides
Agents that affect bacterial nucleic acid synthesis.	Rifampicin, quinolones
Antimetabolites.	Sulphonamides and trimethoprim

2.2.2 Pharmacological sub-groups of antibiotics

For the purpose of this study, the major sub-pharmacological groups of antibiotics reviewed are the penicillins, cephalosporins, carbapenems, aminoglycosides, chloramphenicol, fluoroquinolone, macrolides, tetracycline, sulphonamides and trimethoprim. The subsequent paragraphs summarise the mechanism of action, clinical uses and adverse reactions involving these major groups of antibiotics for systemic use.

2.2.2.1 Penicillins

The penicillin antibiotics were discovered in 1928 from the isolation of a crude preparation from the cultures of *Penicillium notatum*. They constitute natural and semisynthetic antibiotics derived from the fungus. Penicillin consists of a thiazolidine ring attached to a four-membered β-lactam ring with a side chain (Creticos & Sheagren, 1999:249).

- **Mechanism of action**

Penicillins are generally bactericidal. Their mode of action involves inhibiting the transpeptidase enzyme that catalyses the final step in cell wall biosynthesis, i.e. the cross-linking of peptidoglycan, creating weak points by which the cell wall eventually ruptures (Yocum *et al.*, 1980:3977).

- **Adverse effects**

The main adverse effects of penicillins are allergic-hypersensitivity reactions involving anaphylactic reactions, serum sickness, contact dermatitis, phlebitis and direct toxicity (Creticos & Sheagren, 1999:249). Gastro-intestinal disturbances in the form of nausea, vomiting,

epigastric pain, diarrhoea and black ‘hairy’ tongue have been associated with the use of penicillins (Gelone & O’Donnell, 2005:1337).

- **Classification of penicillins**

Penicillins are classified into five main groups, namely the natural penicillins, penicillinase-resistant penicillin, amino-penicillin, extended spectrum penicillin and the beta-lactamase combinations (Gelone & O’Donnell, 2005:1635; McEvoy *et al.,* 2002:321). Table 2.2 provides a general summary of the various clinically used penicillins.

Table 2.2 A summary of the sub-pharmacological groups of penicillins, spectrum of activity and clinical uses

Classification	Antibiotic	Susceptible organisms and clinical indications
Natural penicillin (Geddes & Gould, 2010a:5-38; Geddes & Gould, 2010b:59-56)	Benzyl penicillin – sodium penicillin G, potassium Penicillin G, procaine penicillin, benzathine penicillin G	• They are active against all groups of haemolytic streptococci, *Staphylococcus aureus, Haemophilus influenza gonococci, Treponema pallidum, Anthrax bacillus, Corynebacterium diphtheria.* • Used for penicillin-susceptible pneumococcal infections due to streptococcus, meningococcal infections, syphilis, gonorrhoea, brain abscess, meningococcal and pneumococcal septicaemia, bacterial endocarditis, yaws, rat-bite fever, lyme disease and diphtheria.
	Acid-stable penicillin Phenoxymethyl penicillin (penicillin V), phenoxyethylpenicillin	• *Streptococcus pyogenes, Streptococcus pneumonia,* non-penicillase-producing *Staphylococcus aureus, Staphylococcus viridans, Clostridium* species*, Neisseria gonorrhoea* are all susceptible. • Pharyngitis, scarlet fever, cellulitis, chemoprophylaxis of rheumatoid fever, pneumonia, sinusitis and otitis media.
Penicillinase-resistant penicillin (Turnidge, 2010a: 92; Turnidge, 2010b:100-102; Turnidge, 2010c: 117-119)	Methicillin, nafcillin,	• They are more active in *Staphylococcus aureus, Staphylococcus epidermidis* resistant to penicillin G, *Streptococcus* species, and *Neisseria gonorrhoea*. • *Staphylococcal aureus* infections and coagulase-negative staphylococci infections are treated effectively.
	Oxacillin, cloxacillin, dicloxacillin, flucloxacillin	• *Staphylococcus aureus, Staphylococcus epidermidis* resistant to penicillin G*, Streptococcus* species *Neisseria gonorrhoea*. • Skin and soft tissue infections, endocarditis, pneumonia, cellulitis, due to staphylococcal and streptococcal organisms, surgical prophylaxis, cystic fibrosis, and staphylococcal toxic shock.
Aminopenicillin (Geddes & Gould, 2010c:65-83)	Ampicillin, amoxicillin, becampicllin, betacillin, cyclicillin, pirampicillin,	• *Staphylococcus aureus, Proteus mirabilis, Salmonella typhi, Shigella* Enterococci, *Listeria monocytogenes*, group B streptococci, *Corynebacterium diphtheriae*, *Bacillus anthracis, Streptococcus pyogenes,* and *Streptococcus pneumonia.* • Indications include urinary tract infections due to susceptible organisms, upper respiratory tract infection caused by susceptible organisms, group A streptococci pharyngitis, otitis media, sinusitis, and dental infections.
Extended spectrum (Norrby, 2010a:123-130; Tramontana *et al*., 2010:135-145; Norrby, 2010b:152)	***Carboxypenicillin*** Carbecillin, ticarcillin, carfecillin, carindacillin	• *Pseudomonas aeruginosa, Prevotella* species*, Fusobacterium* species*, Staphylococcus aureus, Streptococcus* species. • Indications include septicaemia and pneumonia or meningitis due to *Pseudomonas aeruginosa*.

Table 2.2 A summary of the sub-pharmacological groups of penicillins, spectrum of activity and clinical uses continued

Classification	Antibiotic	Susceptible organisms and clinical indications
Extended spectrum (Norrby, 2010a:123-130; Tramontana *et al*., 2010:135-145; Norrby, 2010b:152-157)	***Ureidopenicillin*** Mezlocillin, azlocillin, piperacillin, apalcillin	• They are active against *Klebsiella* species, *Escherichia faecalis, Pseudomonas aeruginosa,* and *Bacteroides fragilis*. • They are used for the treatment and prophylaxis of intra-abdominal and pelvis infections, febrile neutropenia, lower respiratory infections, and meningitis.
	Mecillinam and pivmecillinam	• *Escherichia coli, Klebsiella* species*, Salmonella* species*, Yersinia* species*,* and *Citrobacter* species. • They are indicated for urinary tract infections, salmonella infections, chronic bronchitis, and chemoprophylaxis in patients with transurethral prostatic resection.
B-lactamase inhibitors (combined with penicillin) (Norrby, 2010c:168; Rafailidis & Falagas, 2010:204-216; Thursky, 2010:238-249).	Amoxicillin-clavulanic acid	• *Haemophilus influenzae, Staphylococcus aureus,* Beta-lactamase-producing methicillin producing methicillin-sensitive *Staphylococcus aureus*, and *S. epidermidis*, *Neisseria gonorrhoea, Escherichia coli, Moraxella catarrhalis, Proteus,* and *Klebsiella* species. • Otitis media, sinusitis, bronchitis, skin and soft tissue infections, and lower respiratory tract infections.
	Ticarcillin-clavulanic acid	• *Haemophilus influenza, Staphylococcus aureus, Neisseria gonorrhoea, Escherichia coli, Moraxella catarrhalis, Proteus, Klebsiella,* and *Providencia* are susceptible. • They are indicated for mixed aerobic and anaerobic infections.
	Ampicillin-sulbactam	• It is active against *Haemophilus influenzae, Staphylococcus aureus, Neisseria gonorrhoea, Escherichia coli, Moraxella catarrhalis, Proteus, Klebsiella* species*, Bacteroides* species*, Serratia* species*, Acinetobacter baumannii,* and *Citrobacter* species. • It is indicated for bacteraemia, aspiration pneumonia and meningitis caused by mixed aerobic and anaerobic infections, especially with the presence of enterococci, pelvic inflammatory disease, intra-abdominal infections, and diabetic foot infections.
	Piperacillin-tazobactam	• Beta-lactamase producing *Staphylococcus aureus and Staphylococcus epidermidis, Haemophilus influenzae, Neisseria gonorrhoea, Escherichia coli, Moraxella catarrhalis, Proteus* species*, Klebsiella, Bacteroides,* and *Pseudomonas aeruginosa*. • It is indicated for lower respiratory tract infections, gynaecological, skin, soft tissue and intra-abdominal infections, bacteraemia, surgical prophylaxis, and bacterial meningitis *Clostridium difficile* infection.

2.2.2.2 Cephalosporins

Cephalosporins have a broader spectrum of action and inherent resistance to β-lactamase degradation than the penicillins. The first active parent compound used in clinical practice was Cephalosporin C isolated from *Cephalosporium acremonium* in 1948 (Malow & Sheagren, 1999:257-263; Petri, 2001a:1206).

- **Mechanism of action**

The cephalosporins are bactericidal, like the penicillins. Their bactericidal action is mediated by the inhibition of peptidoglycan cross-linkage in the bacteria cell wall (Gelone & O'Donnell, 2005:1642; Malow & Sheagren, 1999:257-263; McEvoy *et al.,* 2002:129).

- **Classification of cephalosporins**

The cephalosporins are classified according to four generations based on their gram-negative spectrum and stability against beta-lactamases (McEvoy *et al.,* 2002:129; Petri, 2001a:1206), namely:

- 1st generation: narrow spectrum of activity and mostly potent against gram-positive organisms and some gram-negative bacilli.
- 2nd generation: extended gram-negative activity and anaerobic organisms.
- 3rd generation: broader spectrum *in vitro* activity against gram-negative bacilli and reduced gram-positive activity.
- 4th generation: gram-negative organisms with multiple resistance and able to cross the blood brain barrier. This group had improved gram-positive activity, while maintaining expanded gram-negative spectrum.

Table 2.3 provides an outline of the generations of cephalosporins, spectrum of activity and clinical indications (adapted from Gelone & O'Donnell, 2005:1642; McEvoy, *et al.,* 2002:139-140; Petri, 2001a:1206).

- **Adverse reactions**

Hypersensitivity reactions in the form of eosinophilia, drug fever, maculopapular rash, urticaria, pruritus, and positive Coomb's test have been reported. Phlebitis associated with the injectable has been commonly associated with cephalosporins. Patients with a history of penicillin allergy have a higher incidence of reactions to cephalosporins (Gelone & O'Donnell, 2005:1642; Malow & Sheagren, 1999:257-263; McEvoy *et al.,* 2002:137-138; Petri, 2001a:1212).

Table 2.3 Generations of cephalosporins, spectrum of activity and clinical uses

Generation	Example	Susceptible organisms and clinical indications
1st	Cephalothin, cephrapirin, cephradine, cephalexin, cefodroxil, and cefazolin.	• *Staphylococcus aureus, Streptococcus pneumonia, Streptococcus pyogenes, Streptococcus epidermidis, Actinomyces* species*, Escherichia coli, Proteus, Klebsiella,* and *Providencia* species. • Treatment of urinary tract infections, respiratory tract infections, orthopaedic and cardiovascular surgical prophylaxis.
2nd	Cefamandole, cefonicid, cefuroxime, cefaclor, cefotetan, cefprozil, ceforamide, cefoxitin, cefmetazole, ceforanid, and loracarbef	• *Haemophilus influenza, Escherichia coli, Proteus, Enterobacter, Klebsiella, Staphylococcus aureus, Citrobacter, Streptococcus pneumoniae, Moraxella catarrhalis, Citrobacter, Acinetobacter, Serratia , Neisseria,* and *Providencia* species. • Treatment of community acquired pneumonia, urinary tract infections by susceptible organisms, otitis media, and sinusitis.
3rd	Cefdinir, cefditonen, cefixime, cefoperazone, cefotaxime, cefpodoxime, ceftazidime, ceftibuten, ceftizoxime, ceftriaxone	• *E. coli, Klebsiella, Enterobacter, Acinetobacter, Serratia, Providencia, Proteus, Morganella* species, *Neisseria gonorrhoea, Bacillus fragilis,* and *Pseudomonas* species. • Meningitis due to susceptible organisms, nosocomial infections, gonorrhoea, pneumonia, and urinary tract infections.
4th	Cefepime	• *Enterobacter, Acinetobacter*, and *Pseudomonas aeruginosa* • Meningitis due to susceptible organisms.

2.2.2.3 Carbapenems and monobactams

Thienamycin was the first carbapenem isolated from *Streptomyces cattleya* (Zhanel *et al*., 2007:1030). Monobactams consist of a β-lactam ring, with a thiazolidine ring and a sulphonate group. Aztreonam, a synthetic member from this group, is resistant to hydrolysis by beta-lactamases (Tattevin *et al.*, 1999:265-271).

- **Mechanism of action**

Carbapenems and monobactams inhibit the formation of intact cell walls by preventing the bacteria from completing transpeptidation of peptidoglycal chains. They bind to different penicillin-binding proteins other than in penicillins and cephalosporins. Imipenem, unlike meropenem and ertapenem, is degraded by the enzyme dehydropeptidase (DHP-1), and therefore it is co-administered with cilastin, which inhibits the enzyme and prevents

nephrotoxicity associated with imipenem (Baba, 2010:458; Petri, 2001a:1213; Tattevin *et al.*, 2005:265-271).

- **Adverse side effects**

The most common side effects of carbapenems and monobactams include hypersensitive reactions, phlebitis, rash, and gastro-intestinal side effects. Carbapenems are also associated with seizures, *Clostridium difficile* colitis, hypersensitive reactions, haematological side effects, hepatotoxicity and nephrotoxicity (Petri, 2001a:1213; Tattevin *et al.*, 1999:265-271).

Table 2.4 provides a summary of the sub-pharmacological groups of carbapenems and monobactams, their spectrum of activity and their clinical uses (adapted from Baba, 2010:458-464; Hayashi & Paterson, 2010:472-475).

Table 2.4 Spectrum of activity and clinical uses of carbapenems and monobactam

Agent	Susceptible organisms	Clinical use
Carbapenem Imipenem, meropenem ertapenem, doripenem, panipenem-betamipron, biapenem.	*Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumonia (penicillin-resistant) Enterococci, Serratia* species, *Klebsiella* species*, Haemophilus* species*, Neisseria* species*, Pseudomonas aeruginosa, Listeria monocytogenes, Acinetobacter* species*, Proteus* species*, Citrobacter* species*, Enterobacter* species*, Bacteroides* species*,* and *Clostridia* species.	Hospital-acquired and healthcare associated pneumonia, complicated urinary tract infections, acute pelvic infection, lower respiratory tract infections, intra-abdominal infections, neutropenic fever, severe diabetic foot infections, and osteomyelitis.
Monobactam Aztreonam	*Escherichia coli, Proteus mirabilis, Klebsiella, Enterobacter, Serratia, Providencia, Citrobacter, Salmonella, Shigella, Edwardsiella, Yersinia* species*, Pseudomonas aeruginosa,* and *Neisseria gonorrhoea.*	Urinary tract infections, skin and skin structure infections, cystic fibrosis, respiratory tract infections, bacterial meningitis, neonatal sepsis, osteomyelitis, bacterial gastroenteritis, malignant otitis externa, otitis media, gonorrhoea and perioperative prophylaxis.

2.2.2.4 Glycopeptides

The glycopeptides, vancomycin, telavancin and teicoplanin, are the clinically relevant forms available for human use (Sulaiman *et al*., 1999:285-289; van Bambeke *et al.,* 2004:914).

- **Mechanism of action**

Glycopeptides inhibit late-stage peptidoglycan synthesis by binding to the bacterial cell wall causing blockade of glycopeptide polymerisation (Allen & Nicas, 2003:513; Kahne *et al*., 2005:432).

- **Spectrum of activity**

Glycopeptides are active against methicillin/oxacillin susceptible *Staphylococcus aureus, coagulase-negative Staphylococcus, Streptococcus pyogenes, Streptococcus pneumonia, Streptococcus agalactase, Clostridium difficile, Propionibacterium, Corynebacterium, Listeria monocytogenes, Actinomyces and Lactobacillus* species (Allen & Nicas, 2003:514).

- **Clinical uses**

Glycopeptides are used to treat potentially life-threatening bacteraemia and endocarditis caused by methicillin resistant *Staphylococcus aureus* (MRSA) and coagulase-negative *Staphylococcus aureus*. It is an alternative therapy for patients allergic to penicillins in the treatment and prophylaxis of endocarditis, pseudomembranous colitis, ventilator associated pneumonia (VAP) susceptible to MRSA and osteomyelitis, meningitis, and *Clostridium difficile*-associated colitis. Telivancin is also used for complicated skin structure infections (van Bambeke *et al.*, 2004:922-3).

- **Adverse effects**

'Red neck' or 'red man syndrome' is the most common side effect of glycopeptides therapy characterised by erythema, flushing or rash over upper torso and face, hypotension, and shock-like symptoms. Local renal toxicities and ototoxicity, cutaneous reactions, and hematologic toxicity are also associated with high plasma concentrations of the drug (McEvoy *et al.,* 2002:474-476; Sulaiman *et al.,* 1999:288).

2.2.2.5. Lipopeptides

Lipopeptides have similar properties to glycopeptides, but have hydrophobic groups, making them less prone to resistance (Allen & Nicas, 2003:512; Arhin *et al.,* 2012:303; Nicasio *et al.*, 2010:654). Table 2.5 is a summary of the sub-pharmacological groups of lipopeptides, their mechanism of action, spectrum of activity and their uses (adapted from Arhin *et al.,* 2012:303; Baltz, 2009:146; Kim *et al*., 2010:647; Straus & Hancock, 2006:1217).

Table 2.5 A summary of the sub-pharmacological groups of lipopeptides

Agent	Mechanism of action, spectrum of activity, clinical uses
Daptomycin	• Daptomycin blocks septum formation caused by lipoteichoic acid. The compound requires calcium ions necessary for the insertion and irreversible binding to the bacterial cytoplasmic membrane. This results in the formation of pores allowing the efflux of potassium ions, depolarising the cell membrane and eventually causing cell death. • Methicillin/oxacillin susceptible *Staphylococcus aureus*, *Enterococci* species, *Clostridium* species, *Corynebacterium*, and *Listeria monocytogenes* are susceptible to daptomycin. • Complicated skin and skin structure infections, staphylococcal bacteraemia, endocarditis, osteo-articular infections, central nervous system infections, community-acquired MRSA infections and respiratory tract infections are effectively treated with daptomycin.
Oritavacin	• Oritavancin inhibits cell wall synthesis by forming complexes with the peptidoglycan chain; this affinity exceeding that of vancomycin. Secondly, ortavancin binds to the cell membrane causing changes in membrane potential and finally disrupting the cell membrane. • Methicillin-resistant/susceptible and vancomycin-resistant *Staphylococcus aureus,* coagulase-negative methicillin resistant/susceptible *Staphylococcus aureus, Streptococcus* species*,* and *Clostridium* species*,* are susceptible to oritavancin. • Oritavancin is useful in complicated skin and skin structure infections and bacteraemia.
Dalbavancin	• Dalbavancin, like the glycopeptides, inhibits peptidoglycan synthesis leading the cell to rupture from changing internal osmotic pressure. • Methicillin susceptible and resistant *Staphylococcus aureus, Streptococcus* species*,* and *Enterobacter* species are all susceptible to dalbavancin. • Skin and skin structure infections and catheter-related bloodstream infections are all successfully treated with dalbavancin.
Telavancin	• Telavancin inhibits cell wall synthesis by interfering with peptidoglycan formation and is ten times more potent than vancomycin. It also binds non-covalently to the cell membrane disrupting the cell membrane and increasing the permeability of the cell, resulting in cell death. • Telavancin is active against *Staphylococcus aureus, Streptococcal* species*, Enterococcus* species*, Actinomyces, Clostridium* species*, Corynebacterium* species*, Lactobacillus* species and *Bacillus anthracis.* • Complicated skin and skin structure infections and nosocomial pneumonia are treated with telavancin.
Ramoplanin	• Ramoplanin sequesters peptidoglycan biosynthesic lipid intermediates, preventing the proper use of these substrates in peptidoglycan synthesis. Owing to this unique mechanism, no cross-resistance has been observed in ramoplanin. • Vancomycin-resistant enterococci, vancomycin-intermediate *Clostridium difficile,* coagulase-negative *Staphylococcus aureus* and vancomycin-resistant *Staphylococcus aureus.* • Complicated skin and skin structure infections and nosocomial pneumonia are treated with ramoplanin.

2.2.2.6 Aminoglycosides

The aminoglycosides consist of highly charged cationic six-membered rings with amino sub-groups having rapid concentration-dependent bactericidal activity against most gram-negative organisms. Members in this group include streptomycin, amikacin, gentamicin, kanamycin, tobramycin, paromomycin, netilmicin, spectinomycin and neomycin. They are either administered by parenteral route (intramuscular, intravenous, intrathecal, intraventricular), or by oral inhalation (kanamycin, tobramycin); neomycin is the only exception administered by oral route (Gilbert, 1999:273-284).

- **Mechanism of action**

Aminoglycosides are bactericidal (dose dependent) and exert their action by irreversibly binding to the 30S ribosomal subunit. This passive ionic interaction between the cationic drug and anionic bacterial cell wall decreases protein synthesis by RNA resulting in cell death. Energy for the uptake phase of the internalisation is dependent on aerobic metabolism; therefore, aminoglycoside has minimum activity against anaerobic organisms. Aminoglycosides also have a post-antibiotic effect depending on the strength used (Chambers, 2001b:1222; McEvoy *et al.,* 2002:1649).

- **Spectrum of action**

Aminoglycosides exhibit *in vitro* activity against a wide range of aerobic gram-negative pathogens, including *Enterobacteriaceae, Pseudomonas* species*, Haemophilus influenzae, Acinetobacter, Proteus, Citrobacter, Escherichia coli* and *Providencia* species (Chambers, 2001b:1222). According to McEvoy *et al*. (2002:1649), *Bacteroides, Entamoeba histolytica, Trichomonas vaginalis,* and *Rickettsia* are all resistant to aminoglycosides.

- **Clinical use**

Aminoglycosides are used concomitantly with extended spectrum penicillin (carbecillin, piperacillin and tazobactam, ticarcillin and clavulanic acid) for the treatment of serious pseudomonal infections owing to the pathogens' potential to exhibit inducible resistance to the β-lactam (Chambers, 2001b:1225; Gelone & O'Donnell, 2005:1650; McEvoy *et al.,* 2002:67).

- **Adverse effects**

Toxicity is likely to occur if treatment is continued for more than ten days. The most common

adverse effects associated with therapy are ototoxicity and nephrotoxicity, mostly occurring in patients with renal impairment, severe dehydration, and those receiving high aminoglycoside dosage, prolonged therapy or in combination with other nephrotoxic or ototoxic drugs. Aminoglycosides also affect the nervous system by causing neuromuscular blockade, apnoea, respiratory depression and respiratory paralysis. Hypersensitive reactions, manifested by rash and drug fever, have also been reported (Chambers, 2001b:1225; Gelone & O'Donnell, 2005:1650; Gilbert, 1999:277; McEvoy *et al.,* 2002:67).

2.2.2.7 Macrolides

Erythromycin, clarithromycin, roxithromycin, dirithromycin, azithromycin, josamycin, midecamycin and spiramycin are useful therapeutic macrolides (Gold & Moellering, 1999:291-297). Gelone and O'Donnell (2005:1652) classify macrolides into three main groups according to the time of discovery and pharmacokinetic profile, as illustrated below:

- Group 1: Erythromycin is the prototype, inhibits cytochrome P450 and has a short duration of action with frequent gastro-intestinal effects.
- Group 2: Clarithromycin has improved spectrum of activity, less gastro-intestinal effects and inhibits cytochrome P450 to a lesser extent.
- Group 3: Azithromycin and dirithromycin do not affect cytochrome P450, they have extended spectrum of action and longer half-lives.

- **Mechanism of action**

Macrolides are bacteriostatic and bind reversibly to the 50S subunit of the bacterial ribosome blocking protein elongation (Chambers, 2001c:1251; Gelone & O'Donnell, 2005:1652).

- **Spectrum of activity**

Macrolides show potent activity against *Streptococcus pyogenes,* β-lactam haemolytic streptococci, *Streptococcus pneumonia, Neisseria gonorrhoea, Neisseria meningitides, Haemophilus ducreyi, Bordetella pertussis, Moraxella catarrhalis,* and *Calymmatobacterium granulomatis* (Chambers, 2001c:1251; Gelone & O'Donnell, 2005:1652).

- **General clinical uses**

Urinary tract infections caused by streptococci, lower respiratory caused by atypical organisms (*Mycoplasma pneumonia, Chlamydia pneumonia, Legionella pneumonia*), community acquired pneumonia (CAP), chancroid, granuloma inguinale, and skin infections caused by susceptible

organisms are successfully treated with macrolides for patients allergic to penicillin. Erythromycin is used for the treatment diphtheria, *Campylobacter jejuni* enteritis, and for the treatment of *Acne vulgaris*. Azithromycin is effective for the treatment of community acquired pneumonia, multidrug resistant shigellosis, non-gonococcal urethritis, cervicitis and pelvic inflammatory disease. Clarithromycin combined with a proton pump inhibitor, treats *Helicobacter pylori* infections, and for *Toxoplasma gondii* when combined with pyramethamine. Spiramycin is suitable for treating toxoplasmosis in pregnancy and prophylaxis against meningococcal disease for persons in close contact with infected patients (Chambers, 2001c:1251; Gelone & O'Donnell, 2005:1652).

- **Adverse effects**

The most common adverse effects are gastro-intestinal disturbances (abdominal cramps, nausea, vomiting), and hepatotoxity, resulting in hepatic cholestasis, especially in the elderly (Chambers, 2001c:1252; Gelone & O'Donnell, 2005:1652-1654).

2.2.2.8 Lincosamides

Lincomycin and clindamycin are the most clinically relevant lincosamides and are functionally related to macrolides.

- **Mechanism of action**

Lincosamides exert their bactericidal action by binding to overlapping sites on the 50S subunits of the ribosome, specifically locating the 23S ribosomal RNA, interfering with protein synthesis (McEvoy *et al.*, 2005:463).

- **Spectrum of activity**

Lincosamides are active against *Enterococcus durans, Bifidobacterium*, *Lactobacillus*, *Eubacterium*, *Propionibacterium*, *Peptococcus*, and *Peptostreptococcus* species, *Actinomyces* species, *Clostridium perfringens*, and *Clostridium tetani, Fusobacterium* species (although *F. varium* is usually resistant), *Prevotella* species, and *Bacteroides* species., including the *B. fragilis* group (McEvoy *et al.*, 2005:463).

- **Clinical uses**

Severe anaerobic infections, abdominal and pelvic abscesses, polymicrobial contagious

infections, *Acne vulgaris*, and prophylaxis of endocarditis are treated with lincosamides. Clindamycin in combination with quinine is indicated for the treatment of *Plasmodium falciparum* infections (McEvoy *et al.*, 2005:468).

- **Adverse drug effects**

Gastrointestinal effects, alteration of bowel flora (overgrowth of the colon by toxigenic *Clostridium difficile*), antibiotic-associated colitis with pseudomembranous formation are the most common side effects associated with lincosamide therapy (McEvoy *et al.*, 2005:468).

2.2.2.9 Tetracycline and related drugs

Tetracyclines are natural and semisynthetic antibiotic derivatives obtained from cultures of *Streptomyces.* They include tetracycline, doxycycline, minocycline and lymecycline (Hooton, 1999:299-301).

- **Mechanism of action**

Tetracyclines inhibit protein synthesis by blocking the binding of amino-acyl-tRNA to the mRNA-ribosome-complex through reversibly binding to the 30S ribosomal subunit. Specificity is highly dependent on selectivity on the bacterial ribosomes required for active energy-dependent transport mechanism into the bacterial cell wall by a system not found in the mammalian cell membranes (Chambers, 2001c:1241; Genole & O'Donnell, 2005:1654; Hooton, 1999:299-301).

- **Spectrum of activity**

Tetracyclines are active against *Mycoplasma, Chlamydia* species*, Balantidium coli, Vibrio* species, *Coxiella burnetii* and *Legionella* species (Chambers 2001c:1240; McEvoy *et al*., 2005:432)*.*

- **Clinical use**

Tetracyclines are indicated for the treatment of rickettsia infections, Q-fever, chlamydial infections, non-gonococcal urethritis, granuloma inguinale, pelvic inflammatory disease, bartonella infections, brucellosis, burkholderia infection, gonorrhoea, plague, tularemia, anthrax, *Acne vulgaris*, community acquired pneumonia, syphilis, Lyme disease, *Helicobacter pylori* infections, cholera, yersinia infections and periodontitis, and travellers' diarrhoea. Doxycycline is used specifically for the prevention of malaria. Minocycline is also used for the treatment of

leprosy (Hooton, 1999:300; McEvoys *et al*., 2005:432).

- **Adverse effects**

The most frequent adverse reactions to tetracyclines are dose related and include gastrointestinal effects (nausea, vomiting, diarrhoea, bulky loose stools, anorexia, flatulence, abdominal discomfort, epigastric burning) and distress. Stomatitis, glossitis, dysphagia, sore throat, hoarseness, black hairy tongue, pancreatitis, and inflammatory lesions in the anogenital region with candida overgrowth have also occasionally been reported (Chambers, 2001c:1246; McEvoys *et al*., 2005:441).

Tetracyclines readily form chelates with multivalent cations (Al^{3+}, Mg^{2+}, Ca^{2+}), and therefore absorption of oral tetracyclines may be impaired in the presence of antacids, iron preparations and laxatives (McEvoys *et al*., 2005:443). They are also avoided in children from birth to eight years, because they form pigments in the developing teething and impair bone growth. These pigments are as a result of the complexes formed from the interaction between the bone salts and tetracyclines.

2.2.2.10 Chloramphenicol

Chloramphenicol was first isolated from *Streptomyces venezuelae*. It is used for severe infections when other effective but less toxic agents cannot be used (Hooton, 1999:301-303).

- **Mechanism of action**

Chloramphenicol inhibits protein synthesis by reversibly binding to the 50S subunit of the bacterial 70S ribosome and consequently preventing the attachment of aminoacyl t-RNA to its binding region. Chloramphenicol is bacteriostatic, but may be bactericidal in high doses or in highly susceptible organisms. It also inhibits mitochondrial protein synthesis in mammalian cells (Chambers, 2001c:1246; Hooton, 1999:301-303).

- **Spectrum of action**

Chloramphenicol is active against *Bacillus fragilis, Bacillus melaningenicus, Clostridium* species*, fusobacterium* species*, Streptococcus pyogenes, Streptococcus pneumonia, Haemophilus influenza, Neisseria gonorrhoea* and *Neisseria meningitides* (Chambers, 2001c:1246).

- **Clinical indications**

Chloramphenicol is useful in the treatment of typhoid fever, rickettsial disease and brucellosis, especially when tetracycline is contraindicated (Chambers, 2001c:1247)

- **Adverse effects**

One of the most serious adverse effects of chloramphenicol is bone marrow suppression due to direct inhibition of mitochondrial protein synthesis causing aplastic anaemia and increasing the risk of leukaemia. Gray syndrome, a type of circulatory collapse, also occurs in premature and new-born infants receiving chloramphenicol (Chambers, 2001c:1246; Hooton, 1999:302).

2.2.2.11 Sulphonamides and trimethoprim

Clinically relevant sulphonamides include sulphamethoxazole, sulphamethizole, sulphadiazine, sulphacytine and sulphisoxazole (Sanche & Ronald, 1999:313).

- **Mechanism of action**

Sulphonamides are structural analogues of para-amino-benzoic acid (PABA) and pteridine, which are precursors to the formation of folic acid necessary for DNA formation in bacteria. Sulphonamides competitively block the production of the intermediary compound, dihydropteroic acid, by interacting with the enzyme dihydripteroic acid synthase (Genole & O'Donnell, 2005:1630; Sanche & Ronald, 1999:313).

Trimethoprim, on the other hand, inhibits the enzyme dihydrofolate reductase (DHFR), which converts dihydrofolic acid into tetrahydrofolic acid (an important precursor in DNA synthesis). Trimethoprim has less affinity for human DHFR, and therefore has minimal effects on human DNA synthesis (Sanche & Ronald, 1999:315).

Sulphonamide and trimethoprim are combined to produce a synergistic effect in a fixed ratio of trimethoprim/sulphamethoxazole (1:5), producing a mean steady-state serum concentration of 1:20 (Petri, 2001b:1172; Sanche & Ronald, 1999:316).

- **Spectrum of activity**

Sulphonamides are active against both gram-positive and gram-negative aerobes, including *Streptococcus pneumonia, Haemophilus influenza, Haemophilus ducreyi, Bordetella pertussis,*

Chlamydia trachomatis, Actinomyces species*, Nocardia asteroides, Plasmodium falciparum, Toxoplasma gondii, Bacillus anthracis, Clostridium tetani,* and *Clostridium perfringens* (Genole & O'Donnell, 2005:1631; Petri, 2001b:1172; Sanche & Ronald, 2005:315).

- **Clinical uses**

The combination of sulphonamide and trimethoprim (also known as co-trimoxazole) is effective in the treatment of acute otitis media, travellers' diarrhoea, shigellosis, respiratory tract infections, brucellosis, burkholderia infections, cholera, cyclospora infections, granuloma inguinale, isosporiasis, treatment and prophylaxis of *Pneumocystis jiroveci*, toxoplasmosis, and Whipple's disease (Petri, 2001b:1177).

- **Adverse effects**

The most frequent adverse effects of co-trimoxazole are adverse gastrointestinal effects and sensitivity skin reactions. Epidermal necrolysis, exfoliative dermatitis, Stevens-Johnson syndrome, serum sickness, and allergic myocarditis are the most severe allergic reactions reported. Hematologic toxicity may occur with increased frequency in folate-depleted patients (Genole & O'Donnell, 2005:1631; Petri, 2001b:1177; Sanche & Ronald, 1999:315).

- **Clinical indications**

Nitro-imidazoles are useful for intra-abdominal infections, *Helicobacter pylori* infections, trichomonas vaginitis, giardiasis, amoebiasis, as well as oral and dental infections (Dow & Ronald, 1999:323; Snyman, 2012:312).

- **Side effects**

The common side effects reported are nausea, anorexia, metallic taste, reversible neutropenia and peripheral neuropathy (Dow & Ronald, 1999:324; Snyman, 2012:312).

2.2.2.12 Fluoroquinolones

The accidental discovery of nalidixic acid from the synthesis of chloroquine has become a progenitor of the quinolones (Norris & Mandell, 1988:2). The quinolones are also referred to as 'fluoroquinolones', '4-quinolones' and 'quinolone carboxylic acid' (Norris & Mandell, 1988:2). In this study, the term 'fluoroquinolone' will be used to refer to this pharmacological group of antibiotics. Fluoroquinolones are part of the few synthetic compounds that possess antibacterial

properties at low eukaryotic toxicity. Domagala (1994:685) is of the view that fluoroquinolones represent a major pharmacological group of antibacterial agents with great therapeutic potentials. Their discovery as antimicrobial agents represents a major advancement in antimicrobial therapy, especially with their anti-pseudomonal property.

2.2.2.12.1 Structural-activity relationship of fluoroquinolones

Various structural features of fluoroquinolones are responsible for their antibacterial efficacy and side effects profile. From Domagala (1994:686), Stahlmann and Lode (1999:305), and Wolfson and Hooper (1985:581), they are:

- The carbonyl and carboxyl groups at positions three and four are important for antibacterial activity because they are responsible for mediating the DNA-gyrase complex.
- The fluorine at position six is essential for high potency of the agent, and halogens at position eight improve the oral absorption and activity against aerobes.
- The cyclopropyl group and amino-acid substituent also improve overall antimicrobial activity.
- Central nervous system (CNS) side effects with theophylline and non-steroidal anti-inflammatory drugs (NSAIDS) and photosensitivity reaction are mainly influenced by the seventh and eighth carbon substituent, respectively.

2.2.2.12.2 Mechanism of action of fluoroquinolones

The fluoroquinolones selectively interact with two bacterial targets, the related enzymes DNA gyrase (topo-isomerase II), an essential bacterial enzyme that keeps the super-helical twists in DNA and involved in DNA replication (Wolfson & Hooper, 1985:581), and topo-isomerase IV, which acts in terminal stages of the separation of the interlinked daughter chromosomes (Hooper, 2001:337). Fluoroquinolones are highly selective in nature. They have a higher affinity for bacterial topo-isomerase compared to that found in humans (Norris & Mandell, 1988:31). Fluoroquinolones form complexes with the two enzymes blocking the movement of the DNA-replication fork, resulting in the inhibition DNA replication (Hooper, 2000:24).

According to King and colleagues (2000), the antibacterial effects of fluoroquinolones continue for two to three hours at sub-inhibitory concentrations after exposure of the bacteria to the drugs. This post-antibiotic effect is increased with longer bacteria-drug exposure and high concentrations of the fluoroquinolones.

2.2.2.12.3 Classification of fluoroquinolones

Since the introduction of fluoroquinolones in the field of medicine, four major classification

systems have been proposed, *viz*. by Andriole and Schellhorn (1997:64); Ball (2000:18); King *et al.* (2000); and Naber and Adam (1998:255). These classifications were based on *in vitro* activity (increasing activity against gram-positive micro-organisms) and clinical indications. Andriole and Schellhorn (1997:64) proposed a classification system for fluoroquinolones (illustrated in Table 2.6) that categorises fluoroquinolones into three major generations (first, early second, late second and third). The classification system by Ball (2000:18-20) is similar to that by Andriole and Schellhorn, but is distinguished by the introduction of a new generation (represented by 3B) with gemifloxacin as an example, having marked activity against gram-positive and atypical respiratory tract infection pathogens.

In 1998, a committee was set up to develop a new system of classifying fluoroquinolones. Naber and Adam (1998:255), appointed by the Paul Erhlich Society for Chemotherapy, recommended a system for classifying fluoroquinolones. Their system grouped fluoroquinolones into four main classes, neglecting the older generations, such as nalidixic acid, cinoxacin, rosoxacin and pipemidic acid. Consequently, two years down the line, King and colleagues' (2000) classification was developed based on Naber and Adam's proposal with the inclusion of the older groups that were neglected (provided in Table 2.7).

Currently, a fifth generation, represented by delafloxacin, is being deliberated on (Somasundaram & Manivannan, 2013:298), but is still undergoing clinical trials (Anon., 2014). It is proven to be more active against gram-positive micro-organisms, especially MRSA (Somasundaram & Manivannan, 2013:298).

Table 2.6 Classification of fluoroquinolones according to three generations (Andriole & Schellhorn)

Generation	General characteristics	Agent
First	They exhibit good gram-negative efficacy and are used for the treatment of urinary tract infections	Nalidixic acid, pipedemic acid, oxolinic acid
Early second	They have broader spectrum of action and show more activity against gram-positive pathogens compared to the first generation.	Norfloxacin, ofloxacin, ciprofloxacin, pefloxacin enoxacin, fleroxacin, lomefloxacin levofloxacin, rufloxacin

Table 2.6 Classification of fluoroquinolones according to three generations (Andriole & Schellhorn) continued

Generation	General characteristics	Agents
Late second	They are also more effective against gram-positive pathogens, especially the pneumococci.	Sparfloxacin, grepafloxacin, tosufloxacin, pazufloxacin, gatifloxacin
Third	They are effective against gram-positive and anaerobic pathogens	Trovafloxacin, moxifloxacin, clinafloxacin, du-6859a

Table 2.7 provides the classification of fluoroquinolones as proposed by King *et al*. (2000).

Table 2.7 Classification of fluoroquinolones in four generation with their various characteristics and antimicrobial spectrum

Generation	Agents	Characteristics	Antimicrobial spectrum
First	Nalidixic acid oxolinic acid pipemidic acid	They are active against gram-negative organisms and are useful in the treatment of urinary tract infections.	*Enterobacteriaceae, Legionella* species*, Mycoplasma* species*, Chlamydia* species*, Haemophilus influenza, Neisseria gonorrhoea, Neisseria meningitides, Moraxella catarrhalis, Rickettsia,* and *Coxiella burnetii.*
Second	Norfloxacin, ofloxacin ciprofloxacin, pefloxacin enoxacin, fleroxacin, lomefloxacin, levofloxacin rufloxacin	They have a broader spectrum of action compared to the first generation, especially against gram-positive organisms.	*Enterobacteriaceae, Legionella* species*, Mycoplasma* species*, Chlamydia* species*, Haemophilus influenza, Neisseria gonorrhoea, Neisseria meningitides, Moraxella catarrhalis, Rickettsia, Coxiella burnetii,* Pseudomonas species, *Staphylococcus aureus,* and *Mycobacterium* species.
Third	Sparfloxacin, grepafloxacin gatifloxacin, tosufloxacin pazufloxacin	They are more effective against gram-positive organisms, especially the pneumococci.	The spectrum of activity is the same as the second generation's, with coverage against penicillin-sensitive and penicillin-resistant *Streptococcus pneumoniae* and extended activity against atypical pathogens.
Forth	Trovafloxacin, moxifloxacin clinafloxacin, DU-6859a	They have better efficacy against gram-positive pathogens and anaerobes and less resistance development.	They are similar to third-generation agents plus broad anaerobic coverage.

From the four recommendations, numerous literature reports have adopted King *et al*.'s view on the four generations of fluoroquinolones (Blondeau, 2004:75; Goldman & Kearns, 2011:3; Liu, 2010:355; Oliphant & Green, 2002:457; Scholar, 2002:165; Sharma *et al.,* 2009:588).

2.2.2.12.4 General pharmacokinetic profile of fluoroquinolones

Fluoroquinolones are rapidly absorbed after oral and parenteral administration. Peak plasma concentrations are reached one to three hours after administration (Scholar, 2003:166; Sharma *et al*., 2009:597). Fluoroquinolones have long elimination half-lives, which permit a once or twice daily dosing regimen (Stein, 1996:19). The presence of food does not affect the bioavailability of fluoroquinolones (Oliphant & Green, 2002:455; Sharma *et al*., 2009:597). The fluoroquinolones' ability to penetrate cerebrospinal fluid is minimal and therefore not used for the treatment of meningitis (Scholar, 2002:166). Protein binding is less than 25%, but higher in enoxacin, but still considered clinically insignificant. Fluoroquinolones undergo renal or hepatic clearance or both (Hooper & Wolfson, 1991:386-387; Oliphant & Green, 2002:455; Scholar, 2002:167). The pharmacokinetic profiles of the sub-pharmacological groups of fluoroquinolones are summarised in Table 2.8.

Table 2.8 A summary of the pharmacokinetics of the relevant fluoroquinolones in clinical practice

Fluoroquinolone	Dose and route of administration	Half-life/hr	Distribution and excretion
Nalidixic acid (McCormack, 2010:1255-1257)	Oral, 1 g four times daily in adults	1.5	It is 93% protein bound and undergoes hepatic conjugation, low tissue concentration except in the urine
Cinoxacin (McCormack, 2010:1255-1257)	Oral, 250-500 mg twice daily; Absorption is poor	1.1-2.7	16-83% protein bound and is excreted unchanged in the urine
Pipemidic acid (McCormack, 2010:1255)	Oral, 500 mg twice daily	3.1	
Ciprofloxacin (McCormack & Grayson, 2010:1278)	Oral, 250-750 mg twice daily; Intravenously, 100-400 mg 12-hourly, 60-70% absorption	3-5	16-40% protein bound, excreted by renal and hepatic mechanisms, 50-75% is excreted unchanged by the kidneys
Enoxacin (Sweetman, 2012)	Oral, 200-400 mg twice daily, bioavailability of 80-90%	3-6	Enoxacin is 18-67% protein bound and is excreted mainly *via* the kidneys
Norfloxacin (Stuart, 2010:1349-1350)	Oral, 400 mg twice daily 30-40% is rapidly absorbed	3-6.5	14% protein bound, metabolised in the liver and mainly excreted via the kidneys.
Ofloxacin (Munckhof, 2010:1367)	Oral and intravenous, 200-400 mg twice daily. Bioavailability is excellent with 95-100% absorption	5-8	Ofloxacin has negligible and excreted via the kidneys
Levofloxacin (Chien *et al.,* 1998:887)	Oral or intravenous 250-750 mg once daily. Bioavailability is more than 95%	6-8	24-38% protein binding and is excreted *via* renal route consisting of glomerular filtration and tubular secretion

Table 2.8 A summary of the pharmacokinetics of the relevant fluoroquinolones in clinical practice (contd.)

Fluoroquinolone	Dose and route of administration	Half-life/hr	Distribution and excretion
Gatifloxacin (Perry *et al*. 2002:172)	Oral and intravenous 400 mg once daily. 96% bioavailability	8-14	20% protein bound and more than 80% is excreted unchanged in the urine
Gemifloxacin (Eliopoulos, 2010:1472)	Oral, 320 mg once daily. The absolute bioavailability is 70%	7-9	61% protein bound and 60% of the drug is excreted into the faeces
Moxifloxacin (Stass *et al*., 1998:2063)	Oral or intravenously 400 mg daily	11-15	40-50% protein bound and eliminated by hepatobiliary metabolism and excretion
Lomefloxacin (Gross & Carbon, 1990:151)	Oral, 400 mg once daily with bioavailability of 95%	6-8	10-15% protein bound and is eliminated by both renal and non-renal mechanisms. Majority of the drug is excreted unchanged in urine

2.2.2.12.5 Clinical uses of fluoroquinolones

The clinical uses of the various sub-pharmacological groups of fluoroquinolones compiled from King *et al*. (2000) and McEvoy *et al*. (2002:764-822) are summarised in Table 2.9.

Table 2.9 Clinical uses of the sub-pharmacological groups of fluoroquinolones

Quinolone	Clinical uses
Nalidixic acid	Uncomplicated urinary tract infections.
Cinoxacin	Uncomplicated urinary tract infections.
Ciprofloxacin	Uncomplicated urinary tract infections, skin and skin structure infections, urethral and cervical gonococcal infection, bone and joint infections, infectious diarrhoea, typhoid fever, and acute sinusitis.
Enoxacin	Uncomplicated and complicated urinary tract infections, urethral and cervical chlamydial and gonococcal infections.
Ofloxacin	Uncomplicated and complicated urinary tract infections, skin and skin structure infections, urethral and cervical gonococcal infection, prostatitis, urethral and cervical chlamydial and gonococcal infections.
Levofloxacin	Uncomplicated and complicated urinary tract infections, acute sinusitis, acute exacerbations of chronic bronchitis, community acquired pneumonia (CAP), skin and skin structure infections, intra-abdominal infections caused by susceptible organisms.
Gatifloxacin	Uncomplicated and complicated urinary tract infections, acute sinusitis, acute exacerbations of chronic bronchitis, and community acquired pneumonia (CAP).
Gemifloxacin	Upper and lower respiratory tract infections, and urinary tract infections.
Trovafloxacin	Complicated urinary tract infections, skin and skin structure infections, urethral and cervical gonococcal infection, prostatitis acute sinusitis, acute exacerbations of chronic bronchitis, and CAP.
Moxifloxacin	Acute sinusitis, acute exacerbations of chronic bronchitis and CAP.
Sparfloxacin	Acute exacerbations of chronic bronchitis and CAP.

2.2.2.12.6 Drug-drug interactions involving fluoroquinolones

Fluoroquinolones are significant antibiotics with a broad antimicrobial spectrum, relatively good pharmacokinetic properties, flexible dosage regimens and few severe adverse effects. However, their clinical uses are adversely affected by some drugs affecting their pharmacokinetic profiles and clinical uses. The subsequent paragraphs discuss the main groups of drugs likely to cause potential drug interactions with fluoroquinolones when administered together.

- **Antacids**

Fluoroquinolones form chelates with multivalent cations such as aluminium ions (Al^{3+}), magnesium ions (Mg^{2+}), and calcium ions (Ca^{2+}), present in antacids and laxatives, resulting in a decrease in oral absorption (Mizuki *et al.*, 1996:48-49). These complexes have reduced lipid-solubility and prevent the absorption of the drug in the gut. Absorption of ciprofloxacin is decreased by 85% and 40% when concomitantly administered with aluminium hydroxide and calcium carbonate tablets, respectively. Norfloxacin absorption is also decreased by 90% when given concomitantly with antacids, and 63% when given five minutes prior to fluoroquinolone administration (Nix *et al*., 1990:434). The oral absorption of gatifloxacin is reduced by 45%, 68% and 18%, respectively, when given two hours prior, concomitantly, and two hours after with the administration of an aluminium containing antacid (Lober *et al.*, 1999). Stahlmann & Lode (2000:438) recommend the avoidance of antacids for peptic ulcer treatment in patients receiving fluoroquinolones. However, if avoidance is inevitable, the fluoroquinolones must be taken first in the morning, and the antacid two to six hours later.

- **Oral iron preparations**

Ferrous sulphate and ferrous fumarate preparations have been found to decrease fluoroquinolone absorption by 64% and 70%, respectively (Mizuki *et al*., 1996:48-49; Rodriquez *et al.*, 1999:240).

- **Sulcralfates**

Sulcralfates consist of poorly absorbed basic aluminium salts of sucrose octasulfate, which form chelates in the presence of fluoroquinolones. Administration of sulcralfates two hours prior to and concomitantly with enoxacin decreased oral absorption by 43% and 98%, respectively (Brouwers*,* 1992:271; van Slooten *et al*., 1991:580).

- **Acid secretion suppressants**

The use of histamine (H_2)-receptor antagonists, e.g. ranitidine and cimetidine has no effect on the oral bioavailability on fluoroquinolones (Nix, 1990:434). However, the absorption of enoxacin is reduced by 25% in the presence of ranitidine, because it requires an acidic medium for maximal absorption. Patients should be advised to avoid metal-containing drugs if fluoroquinolone therapy is to be initiated. If acid secretion suppression is required, an H_2-receptor antagonist or a proton pump inhibitor (PPI) can be used (Brouwers*,* 1992:272; Stass *et al.,* 2001:45).

- **Xanthine derivatives**

The concentration of theophylline is increased due to reduced clearance, prolonging the half-life ($t_{1/2}$). This effect leads to severe adverse effects involving the central nervous system (CNS), e.g. seizures. This marked increase has been found with concurrent administration of theophylline and either ciprofloxacin or pefloxacin with a reduction in clearance of 30.4% and 29.4%, respectively (Mizuki *et al.*, 1996:48-49; Staib *et al*., 1989:292).

The clearance of caffeine is also reduced in the presence of fluoroquinolones. Enoxacin has been found to decrease caffeine clearance by 79%, which results in more adverse events involving the CNS and gastro-intestinal tract (Staib *et al*., 1987:172).

- **Non-steroidal anti-inflammatory drugs (NSAIDs)**

Fluoroquinolones inhibit the binding sites for gamma-aminobutyric-acid (GABA) in a dose-dependent manner resulting in the excitation of the CNS (Akahane *et al*., 1994:2328; Sergev *et al*., 1988:1626). According to Hori *et al*. (2003:317), the order of potency of the inhibition of GABA receptor binding is norfloxacin> nalidixic acid> enoxacin> ofloxacin> ciprofloxacin. The decrease in neuron response to GABA can be associated with the piperizine ring present in the structure of fluoroquinolones.

2.2.2.12.7 Adverse drug reactions associated with fluoroquinolones

The major side effects associated with fluoroquinolones vary in incidence, severity and are dependent on the structural configuration of the fluoroquinolone. The major effects are:

- Gastro-intestinal effects involving nausea (Lober *et al*., 1999:1069), vomiting, dyspepsia and abdominal pain (Stass & Kubitza, 1999:85).
- Central nervous system (CNS) effects involving headaches (Stass *et al*., 1998:2062)

dizziness, tiredness and sleepiness (Saravolatz & Legget, 2003:1213).

- Hypersensitivity reactions involving erythema, pruritus, urticaria and rash.
- Photosensitivity reactions.
- Arthralgia.
- Tendonitis was first reported in pefloxacin. It affects the Achilles tendon and can be bilateral leading to rupture occurring mostly in elderly patients on corticosteroid therapy and renal failure (Meyers *et al*., 2013:229).
- Cardiac effects: Grepafloxacin has been reported to cause prolongation of the QT interval resulting in arrhythmias and *torsades de pointes,* and therefore has been withdrawn from the market. The uses of gatifloxacin and moxifloxacin have also been reported to cause arrhythmia (Lapi *et al.,* 2012:1460).
- Peripheral neuropathy: Cohen (2001:1541-1543) reviewed forty-five cases presented in articles about the neurotoxicity and musculoskeletal effects of fluoroquinolones. All patients reported at least one event involving the peripheral nervous system characterised by tingling, numbness, pricking, burning sensation, pins/needles sensation, skin crawling sensation and numbness.

2.2.2.12.8 Use of fluoroquinolones in children less than eighteen years

Fluoroquinolones in pre-clinical studies were found to induce changes in the immature articular cartilage of the weight-bearing joints of young laboratory animals (Burkahdt *et al*., 1997:1199; Gough *et al*., 1992:444). There are controversies with regard to the use of fluoroquinolones in children below the age of 18 due to this safety warning, limiting its use (Goldman & Kearns, 2011:2; Kline *et al*., 2012:56). Despite the concerns raised on the adverse events presumed in this population, there have been reports of fluoroquinolone prescriptions for this age group (Arguedas *et al*., 2003:953; Cao *et al*., 1999:247; Chalumeau *et al*., 2003:717). Table 2.11 provides a summary of studies evaluating the use, effectiveness and safety of fluoroquinolones in patients below the age of 18 years. These studies concluded recommending the use of fluoroquinolones in this age group owing to their efficacy and low incidence of adverse effects, especially arthralgia.

In 2006, the Committee on Infectious Diseases (2006:1290) recommended the use of fluoroquinolones in children below 18 years in infections caused by MDR pathogens for which there are no safer and more effective alternatives. Additionally, they have been indicated when therapies by parenteral route are not possible and there are no other agents available. This recommendation was based on the evaluation of several studies (refer to Table 2.11), which reported the incidence of mild to moderate adverse events. The appropriate use of

fluoroquinolones in children younger than 18 years is limited to the following indications recommended by Committee on Infectious Diseases (2006:1290):

- Treatment of inhalational anthrax.
- Urinary-tract infections caused by *Pseudomonas aeruginosa* or MDR pathogens.
- Chronic pus-producing otitis media or malignant otitis externa caused by *Pseudomonas aeruginosa.*
- Exacerbation of pulmonary disease in cystic fibrosis.
- Mycobacteria infections.
- Gastro-intestinal infections caused by MDR *Shigella, Salmonella typhi* and *Vibro cholera.*
- Life-threatening infections caused by fluoroquinolone-susceptible bacteria in children who are allergic to safer alternative treatments.
- Documented bacterial septicaemia or meningitis caused by bacteria with *in vitro* resistance to approved therapy or in immuno-compromised children in whom there has been treatment failure in approved therapies.

The recommended dosage in children younger than 18 years in diagnoses for which fluoroquinolone is indicated is provided as follows in Table 2.10 (compiled from the BNF for Children, 2012:302-303; Taketomo *et al*., 2010:853, 1013).

Table 2.10 Approved fluoroquinolone dosage regimen in children younger than 18 years

Fluoroquinolone	Indication and dosage
Ciprofloxacin	**UTI**
	By mouth: in neonates 10 mg/kg 12 hourly; child (1 month to 18 years 10 mg/kg 12 hourly, dose doubled in severe infections (max. 750 mg 12 hourly).
	By intravenous infusion over 60 minutes: in neonates 6 mg/kg 12 hourly; child (1 month to 18 years) 6 mg/kg 8 hourly increased to 10 mg/kg 8 hourly in severe infections (max. 400 mg every 8 hours).
	Severe RTI/GI Infections
	By mouth: in neonates 15 mg/kg 12 hourly; child (1 month to 18 years) 20 mg/kg 12 hourly (max. 750mg 12 hourly).
	By intravenous infusion over 60 minutes: in neonates 10 mg/kg 12 hourly; child (1 month to 18 years) 10 mg/kg 8 hourly (max. 400 mg every 8 hours).

Table 2.10 Approved fluoroquinolone dosage regimen in children younger than 18

years (contd.)

Fluoroquinolone	Indication and dosage
Ciprofloxacin	**Pseudomonal LRTI in cystic fibrosis**
	By mouth: child (1 month to 18 years) 20 mg/kg 12 hourly (max. 750 mg 12 hourly).
	By intravenous infusion over 60 minutes: child (1 month to 18 years) 10 mg/kg 8 hourly (max. 400 mg every 8 hours).
	Anthrax (treatment and post-exposure prophylaxis)
	By mouth: child (1 month to 18 years) 15 mg/kg (max. 500 mg) 12 hourly.
	By intravenous infusion over 60 minutes: child (1 month to 18 years) 10 mg/kg (max. 400 mg) 12 hourly.
Levofloxacin	6 months to 5 years: 10 mg/kg/day every 12 hours
	Children older than 5 years: 10 mg/kg/day every 12 hours (maximum dose 500 mg)
Ofloxacin	Children older than 1 year: 15 mg/kg/day divided every 12 hours

Table 2.11 Studies evaluating the effectiveness of fluoroquinolones and incidence of arthropathy in children younger than 18 years

Year	Location	Number of patients and age	Drug therapy	Indication	Causative organism	Cure rate	Arthropathy reported	Reference, year
1992 to June 1998	United States	7897 0-18 years	Ciprofloxacin, levofloxacin and ofloxacin compared with azithromycin	UTI and skin and skin structure infections	Not stated	Not evaluated	There was <1% incidence of arthropathy	Yee *et al*. (2002)
1994	Not stated	1795 0-18 years	Ciprofloxacin	RTI, pneumonia, cystic fibrosis, bronchitis	*Pseudomonas aeruginosa* and *Staphylococcus aureus*	Not evaluated	29 cases reported, of which 25 (86%) were resolved	Hampel *et al*. (1997)
July 1995 to August 1996	Vietnam	82 younger than 15 years	Ofloxacin compared with cefixime	Uncomplicated typhoid fever	*Salmonella typhi*	97% cure rate with ofloxacin as opposed to 75% in cefixime	Not evaluated	Cao *et al*. (1999)
May 1996 to June 2000.	Zimbabwe, South Africa and Bangladesh	253 1-12 years	Ciprofloxacin therapy for 3 days compared with 5 days therapy	Dysentery	*Shigella dysenteriae*	65 and 69% cure rate for short-term and long-term therapy, respectively.	8 reported cases of arthralgia	The Zimbabwe, Bangladesh, South Africa Dysentery Study Group (2002)
April 1998 to July 1999	North, Central and South America, Egypt, South America and Hungary	311 3 months to 12 years	Trovafloxacin compared with ceftriaxone	Meningitis	*Neisseria meningitides* and *Haemophilus influenza.*	Cure rates for trovafloxacin and ceftriaxone were 75% and 71%, respectively.	Arthropathy reported in trovafloxacin group was 1% compared to 4% in the ceftriaxone group	Saez-Llorens *et al.* (2002)

Table 2.11 A review of studies evaluating the effectiveness and incidence of arthropathy in children less than eighteen years (continued)

Year	Location	Number of patients and Age	Drug therapy	Indication	Causative organism	Cure rate	Arthropathy reported	Reference, year
May 1998 to September 2000	France	276 Children younger than 19 years	All fluoroquinolones prescribed during the study period	Cystic fibrosis, urinary tract infection, gastro-intestinal infections, bone and joint infection	*Salmonella typhi Shigella*.	Not evaluated.	Incidence of arthropathy less than 3.8%.	Chalumeau *et al*. (2003)
Not stated	United States, Costa Rica, Panama, Argentina, Thailand and Venezuela.	115 6-48 months	Gatifloxacin, 10mg/kg/day for 10 days.	Recurrent acute otitis media	*Haemophilus influenza, Moraxella catarrhalis, Streptococcus*	86% cure rate	There were no reported cases of arthropathy	Arguedas *et al*. (2003)

2.3. Antimicrobial resistance

2000 B.C. – Here, eat this root
1000 A.D. – That root is heathen. Here, say this prayer
1850 A.D. – That prayer is superstition. Here, drink this potion
1920 A.D. – That potion is snake oil. Here, swallow this pill
1945 A.D. – That pill is ineffective. Here, take this penicillin
1955 A.D. – Oops... bugs mutated. Here, take this tetracycline
1960-1999 A.D. – More "Oops"... Here, take this powerful antibiotic
2000 A.D. – The bugs have won, that antibiotic doesn't work anymore. Here, eat this root
Anonymous

Antimicrobials have been beneficial in saving lives, resulting in a significant reduction in morbidity and mortality due to infectious diseases and have allowed major advances in surgery. However, this unrealistic expectation with antibiotics having a magical ability to prevent or cure infectious disease without the eventual loss of activity has led to overuse and misuse globally (Kunin, 1995:107).

The concern about antibiotic resistance was raised by Sir Alexander Fleming (1945:9) when he discovered penicillin. He remarked that *"The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily under dose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant."* Walsh (2000:776) also rightly indicated that, *"Once an antibiotic is proven to be effective and enters widespread human therapeutic use, its days are numbered."* Presently, antimicrobials are the only class of drugs that have become obsolete from use (WHO, 2012:33).

2.3.1 Definition of antimicrobial resistance

An organism is said to be resistant if it has the capacity to proliferate in the presence of the antimicrobial agent it was originally sensitive to (WHO, 2001:15). Resistance renders standard treatments ineffective, causing an increase in the prevalence of infections and the risk of spread to others.

2.3.2 Risk factors for emergence of antimicrobial resistance

Many of the antibiotics available presently are no longer effective due to emerging resistance caused by the following factors (Cohen, 1992:1053; Essack, 2006:51c; Harbath & Samore, 2005:794-795; Laxminarayan *et al.,* 2013):

- The characteristics of micro-organisms: Ability to exchange genetic material, having inherent resistance, ability to survive changing environmental conditions, occupy certain ecological niches, colonise and infect.
- Environmental or human reservoirs in which resistant organisms are present.
- Selective pressure influenced by patterns of antimicrobial prescribing and use: Inappropriate use by physicians and patients, self-prescription, poor quality of antimicrobial agents through counterfeit sales and dispensing by unauthorised personnel, long-term use posing high risk of resistance, especially in developing countries.
- Societal and technological changes: Lack of standard treatment guidelines in healthcare facilities, lack of training for prescribers, pressures from the pharmaceutical industry.
- Poor infection control surveillance systems: Inadequate logistics and equipment, and the lack of trained professionals to monitor the spread of nosocomial infections pose a huge setback in the curbing of antimicrobial resistance.
- Lastly, poverty has been cited as a probable cause for the emergence and spread of antimicrobial resistance. There is a lack of access to good healthcare, clean food and water, good sanitation in most middle-income and developing countries, also rendering the outbreak of infections and resistant strains.

2.3.3 Mechanisms of antimicrobial resistance

Resistance can be intrinsic or acquired (Sefton, 2002:560). Intrinsic resistance is a natural phenomenon occurring in the absence of antimicrobial use; this implies that not all micro-organisms are intrinsically susceptible to all antimicrobials. Acquired resistance refers to adaptive mechanisms formed by micro-organisms in response to changes in the environment; or the acquisition of genetic materials to form resistant genes (Sefton, 2002:560). Antimicrobial resistance involves six major mechanisms (Denis *et al.,* 2010:91; Sefton, 2002:560), namely:

- Active expulsion of antibiotic from the bacterial cell by trans-membrane efflux system.
- Modification of the bacterial cell envelope rendering it less permeable to the drug.
- Modification of target site.
- Production of protective proteins at target site.
- Inactivation of the drug by specific enzymes before or after the drug enters the cell of the bacterium.
- Acquisition of target by-pass by a unique metabolic pathway.

Most micro-organisms employ more than one mechanism as defence in the presence of antibiotics. The development of antibiotics has also been successful through the exploitation of these mechanisms used by micro-organisms.

The subsequent paragraphs briefly describe the six main mechanisms of antimicrobial resistance with some examples.

2.3.3.1 Efflux-mediated antimicrobials resistance

The first energy-dependent export of antimicrobials from bacteria that was first reported in tetracyclines (Ball *et al*., 1980:12) is also seen in fluoroquinolones (Jacoby, 2005:121). The efflux system falls into five categories, namely:

- **Major facilitator super family (MFS):** The efflux pump genes coded as Bmr, pmrA, NorA have been isolated in *Bacillus subtilis* (Neyfahk *et al*., 1991:4785), *Streptococcus pneumonia* (Gill *et al*., 1999:189; Piddock *et al.*, 2002:812), and *Staphylococcus aureus* (Kaatz *et al*., 1993:1093), respectively mediating resistance to chloramphenicol and quinolones. The efflux pump gene, LrfA, has also been identified in a study in *Mycobacterium segmatis* (Takiff *et al.*, 1996:366) to simulate *Mycobacterium tuberculosis* resistance in quinolones.
- **ATP-binding cassette family (ABC):** The ABC multidrug transporters are more characterised in gram-positive organisms (Davidson & Chen, 2004:242). They are found in *Vibrio cholera, Staphylococcus marcescens, Staphylococcus enteritis* and *Clostridium hathewayi*. This system has also been cited to be responsible for fluoroquinolone resistance.
- **Resistance nodulation division (RND):** The RNDs are found in the inner membrane of the bacterial cell and their main functions are to transport substrates into the cells (Blair & Piddock, 2009:512). The efflux systems encoded by the specific operons in *Pseudomonas aeruginosa* and *S. maltophilia*, expressed by the mutational genes, are responsible for quinolone resistance (Poole, 2000:2235-2237).
- **Small multidrug resistance (SMR):** Confer resistance to a number of quaternary ammonium compounds (QAC) (Bay *et al.*, 2008:1816; Paulsen *et al.,* 1996:590-592).
- **Multidrug and toxic compound resistance (MATE):** Fluoroquinolone resistance reported in *Campylobacter, Citrobacter, Enterobacter, Escherichia coli, Klebsiella, Proteus* and *Pseudomonas* species is determined by a three-component efflux system encoded by specific genes (Poole, 2005:21).

2.3.3.2 Alterations in cell wall structure

Gram-negative bacteria have a unique permeability barrier known as the outer membrane. This layer consists of proteins responsible for transport activities and delimits a zone outside the cytoplasm conferring passage selectivity (Sefton, 2002:560). Diffusion of hydrophobic drugs such as macrolides and β-lactams through porin channels of the outer membrane is relatively poor. From a study by Nikaido (1989:1832), the permeability of cephalosporins in *Pseudomonas*

aeruginosa is two times less than that of *Escherichia coli.* Decreased permeability can be due to the following factors (Nikaido, 1989:1832):

- **Porin deficiency mutants:** The loss of porins as observed in gram-negative bacteria may decrease the uptake of many hydrophilic drugs across the outer membrane causing multi-drug resistance, e.g. imipenem resistance as seen in *Pseudomonas aeruginosa*.
- **Mutations involving specific pathways:** Bacteria produce specific pathways for the transport of essential nutrients. Some antibiotics have been designed specifically to use specified pathways in the outer membrane.

2.3.3.3 Target site mutation

Mutations occur at different sites of the bacteria genome and based on the origin of the mutated gene. The determinants of resistance can be classified as: acquisition of foreign DNA (transduction, transformation and conjugation), mutation of pre-existing genetic determinants and mutation on acquired genes (Sefton, 2002:561; Spratt, 1994:388). Examples include DNA gyrase-determined resistance to fluoroquinolones, ribosomal resistance to streptomycin through alteration of a single amino-acid at the target site, penicillin resistance due to modified penicillin-binding proteins, and sulphonamide and trimethoprim resistances due to altered dihydropteroate synthase and dihydrofolate reductase, respectively (Denis *et al.,* 2010:99-100).

Resistance in the quinolones is due to the alteration of DNA-gyrase, which has two subunits, namely A and B, and DNA topo-isomerase IV, occurring within a domain referred to as the fluoroquinolones resistant determining region (QRDR) (Hooper, 1999:38; Hopkins *et al*., 2005:360-362; Nakamura, 1997:128). According to Spratt (1994:389-390), resistance to sulphonamides and trimethoprim in *Staphylococcus aureus* occurs by the organisms obtaining a gene encoding to a new target enzyme that has lower affinity to the antibiotic than the original enzyme.

2.3.3.4 Protection of target site by proteins

The gene found to be responsible for the PMQR (plasmid-mediated quinolone resistance) has been proven in studies to protect DNA-gyrase from being inhibited by the fluoroquinolones, but unable to protect topo-isomerase IV (Martinez-Martinez *et al*., 1998:797). The mfpA gene has been found to influence intrinsic resistance to *Mycobacterium smegmatis*. When the gene is overexpressed, resistance to ciprofloxacin and sparfloxacin is increased (four- to eight-fold rise in MICs) in *Mycobacterium smegmatis* and *Mycobacterium bovis* (Cremet *et al*., 2011:154). Cremet and his co-workers (2011:155) later discovered other PMQR genes, namely aac(6')-ibcr and qepA. PMQR have also been reported in Italy (Longhi *et al.*, 2012:1921), Japan (Saga *et*

al., 2007:799; Saito *et al*., 2007:601), the United Arab Emirates (Jacoby *et al.*, 2003:560), South Africa (Govender *et al.,* 2009:1313; Keddy *et al.,* 2010:879) and China (Wang *et al*., 2003:2242).

2.3.3.5 Modifying enzymes

Enzymes involved in resistance mechanisms are either mediated by the plasmid or chromosome (Sefton, 2002:560). Beta-lactamase production is the main cause of resistance in *Staphylococcus aureus*, *Haemophilus influenzae*, *Moraxella catarrhalis, Neisseria gonorrhoea* and enteric gram-negative rods (Wright, 2005:1462). Some beta-lactam drugs such as flucloxacillin are stable against the β-lactamases produced by *Streptococcus aureus,* whereas the newer cephalosporins are stable against many of the β-lactamases produced by these organisms (Wright, 2005:1460). Other examples include aminoglycoside modifying enzymes and chloramphenicol actelytransferases conferring resistance to aminoglycosides and chloramphenicol, respectively (Sefton, 2002:560).

2.3.3.6 Acquisition of a target by-pass system

In sulphonamides and trimethoprim, for example, a target by-pass system, which confers resistance, is formed by the mediation of the enzymes – dihydropteroate synthase and tetrahydrofolate reductases, respectively (Sefton, 2002:560). The presence of PB2′ found in methicillin-resistant *Staphylococcus aureus* (MRSA) renders the organism resistant to flucloxacillin, because it binds loosely to β-lactams (Sefton, 2002:560).

2.3.4. Antibiotic resistance patterns

The tremendous increase in trade and human mobility brought about by globalisation has enabled the rapid spread of infectious agents, especially drug-resistant strains. While developed countries are able to afford the latest antibiotics to treat resistant infections, those in the developing world have limited access to life-saving drugs in the combat against resistant infections (WHO, 2001:11). The spread of antimicrobial resistance is not crippled by boundaries. For example, in November 2013, New Zealand (one of the tightly quarantined nations) reported the first death resulting from a totally drug-resistant bacterium known as ”KPC-Oxa 48” from a Vietnamese male patient (McKenna, 2013). There is no country, however effective they are in containing resistance within its boundaries, which can protect itself from the importation of resistant bacteria through travel and trade (WHO, 2001:11).

Africa, and South Africa for that matter, is faced with a huge infectious disease burden where

respiratory, meningeal and sexually transmitted diseases are highly prevalent (Crowther-Gibson *et al*., 2011:567). Resistant strains of organisms already identified in South Africa, include:

- Multi-drug resistant *Streptococcus pneumonia,* which is resistant to penicillins, macrolides, chloramphenicol, fluoroquinolones (von Gottberg, 2008:328) and co-trimoxazole (Appelbaum, 1992:77);
- Methicillin-resistant *Staphylococcus aureus* (MRSA) (Marais *et al*., 2009:171);
- Ciprofloxacin-resistant gonococci (Lewis, 2007:1149);
- Carbapenem-resistant *Klebsiella pneumonia, Enterobacter* species*,* and *Pseudomonas aeruginosa* (Brink *et al*., 2012:599);
- New Delhi metallo-beta-lactamase (NDM) resistance in Enterobacteriaceae (Lowman *et al.*, 2011:874), and
- MDR *Mycobacterium tuberculosis* (Brink *et al*., 2008:586).

Among the countries in Africa, South Africa has the most active surveillance system on antibiotic resistance (Gelband & Duse, 2011:553). The National Antibiotic Surveillance Forum (NASF) and the Group for Enteric Respiratory and Meningeal disease Surveillance in South Africa (GERM-SA) are two highly recognised bodies in the public sector responsible for the monitoring of resistance patterns. In the private health sector, the Federation of Infectious Diseases Societies of South Africa (FIDSSA) conducts surveillance on several pathogens in infectious diseases (Gelband & Duse, 2011:553).

Table 2.12 provides antimicrobial susceptibility data of some clinically important pathogens identified in public hospitals from Johannesburg, Pretoria, Bloemfontein and Cape Town in 2010 (adapted from Bamford *et al*., 2011).

Table 2.12 Susceptibility patterns of relevant micro-organisms in South Africa for 2010

	Susceptibility of organism/%					
Drug	*Escherichia coli*	*Klebsiella* species	*Enterobacter* species	Drug	*Pseudomonas aeruginosa*	*Acinetobacter baumannii*
Gentamicin	82	43	73	Piperacillin/ tazobactam	45	9
Amikacin	90	81	90	Cefepime	67	18
Ciprofloxacin	82	63	89	Ceftazidine	74	37
Ertapenem	100	98	96	Imipenem	66	21
Imipenem	100	100	96	Meropenem	68	20
Meropenem	100	100	100	Gentamicin	69	25
				Amikacin	73	37
				Ciprofloxacin	69	39

The susceptibility patterns for *Staphylococcus aureus* for cloxacillin, erythromycin and clindamycin were 55, 54 and 73%, respectively (Bamford *et al*., 2011). This study confirms the prevalence of resistant strains of micro-organisms affecting healthcare centres in South Africa.

In Table 2.13, the resistance patterns of some clinically relevant bacteria are outlined, analysing country-specific trends. These studies reveal the incidence and prevalence of resistant micro-organisms in Sub-Saharan Africa. There is confirmation in the emergence and increase in resistance to conventional therapies and newer drugs, for example third generation cephalosporins (ceftriaxone) and fluoroquinolones. The need to monitor resistance patterns is therefore crucial in defining the prognosis of bacterial infections.

Table 2.13 An overview of the resistance patterns of clinically relevant micro-organisms in Africa

Location	Inception Year	Organism	Source of isolate	Number of isolates	Results	Reference, year
Nigeria	1987-1992	*Neisseria meningitides*	Isolates were from CSF of children and adults	289	Prevalence of strains resistant to ampicillin, penicillin and co-trimoxazole increased from 7 to 75%, 14 to 75% and 39 to 87%, respectively	Emele (2000)
South Africa	1991-1998	*Streptococcus pneumonia*	Isolates were from the blood or CSF, population was not defined	7 406	Multidrug resistance increased from 19 to 25% Resistance to penicillin increased from 9.6 to 18%	Huebner *et al.* (2000)
Morocco	1992-2000	*Neisseria meningitides*	Isolates were from the blood and CSF of children, ages not specified	163	4.3% of strains identified as multidrug-resistant	Zerouali *et al.* (2002)
Ghana	January 1994 to June 1996	*Escherichia coli* *Streptococcus pneumonia* *Staphylococcus aureus*	The strains were isolated from wounds, urine, ear, nose, throat, sputum and aspirates, the population was not specified	11 380	88% resistant to ampicillin 82% resistant co-trimoxazole 30.6% resistant to penicillins 21.7% resistant to chloramphenicol 18% resistant to flucloxacillin	Ohene (1997)
Kenya	1994-2002	*Haemophilus influenza*	Isolates were cultured from the blood or CSF from patients in the paediatric ward	240	Resistance to trimethoprim/sulfamethozaxole increased from 6 to 27% Resistance to amoxicillin and chloramphenicol increased by 11% and 2%, respectively.	Scott *et al.* (2005)

Table 2.13 An overview of the resistance patterns of clinically relevant micro-organisms in Africa (continued)

Location	Inception Year	Organism	Source of isolate	Number of isolates	Results	Reference, year
Ivory Coast, Morocco, Senegal, Tunisia	1996-1997	*Streptococcus pneumonia*	Isolates were from CSF, blood and pus, population not stated	375	30% of isolates resistant to penicillin G 3.7% were resistant to amoxicillin 7.3% were resistant to cefotaxime-ceftriazone 8.6% were resistant to chloramphenicol 28% were resistant to erythromycin 38.3% were resistant to tetracycline 2.1% were resistant to rifampicin 36.4% were resistant to co-trimoxazole	Benbachir *et al*. (2001)
Sub-Saharan Africa	1996-1997	Methicillin-resistant *Staphylococcus aureus* (MRSA)	The strains were isolated from surgical swabs and pus, blood and urine, population was not defined	1 440	26% prevalence in Nigeria 27.7% prevalence in Kenya 21.3% prevalence in Cameroun 14.4% and 12.5% in Morocco and Senegal, respectively	Kesah *et al.* (2003)
Algeria	1996-2000	*Streptococcus pneumonia*	Isolates were from CSF, blood and pus, from children ages not specified	309	33% resistant to penicillin G	Ramdani-Bouguessa & Rahal (2003)
Gambia	1996-2003	*Streptococcus pneumonia*	The isolates were obtained from children aged younger than 6 years with the infection during a *Haemophilus influenzae* vaccine effectiveness study and patients with invasive pneumococcal disease	531	1% resistant to trimethoprim/sulphadoxine, tetracycline and chloramphenicol from 1996 to 2000. 3% were resistant to trimethoprim/sulphadoxine, tetracycline and chloramphenicol from 2000 to 2003.	Adegbola *et al.* (2006)

Table 2.13 An overview of the resistance patterns of clinically relevant micro-organisms in Africa (continued)

Location	Inception Year	Organism	Source of isolate	Number of isolates	Results	Reference, year
Egypt	1998-2003	*Streptococcus pneumonia*	Not specified	205	6% were resistant to ceftriazone 52% were resistant to tetracycline 59.7% were resistant to trimethoprim 11% were resistant t erythromycin 9% were resistant to chloramphenicol	Wasfy *et al.* (2005)
Ethiopia	2000	*Neisseria gonorrhoea*	Isolates were from males with urethral discharge	142	92% resistant strains were identified in co-trimoxazole 87.5% were multidrug resistant	Tadese *et al.* (2001)
South Africa	2000-2006	*Streptococcus pneumonia*			18% were resistant to levofloxacin	von Gottberg *et al.* (2008)
South Africa	2003 to January 2005	*Neisseria gonorrhoea*	The strains were isolated from men and women with urethral and vaginal discharge, respectively	415	Ciprofloxacin-resistant strains increased from 24 to 42%	Moodley *et al.* (2001)
South Africa	2003-2007	*Salmonella typhi*	Not specified	510	Prevalence of nalidixic resistant strains was 5%	Smith *et al.* (2010)
Malawi	May-August 2007	*Neisseria gonorrhoea*	Isolates were from men with urethral discharge	126	19 and 77% of strains identified as penicillin- and tetracycline resistant, respectively	Brown *et al.* (2010)
Ethiopia	September 2007 to January 2012	*Streptococcus pneumonia*	Isolates were from patients who visited the hospital	153	11% were resistant to ciprofloxacin 9.8% were resistant to ceftriaxone 31% were penicillin and tetracycline	Anagaw *et al.* (2013)
South Africa	2009	*Neisseria meningitides*	The strain was isolated from the CSF of a Zimbabwean lady	1	The first isolation of plasmid fluoroquinolone-resistant strains	Du Plesis *et al.* (2010)

Table 2.13 An overview of the resistance patterns of clinically relevant micro-organisms in Africa (continued)

Location	Inception Year	Organism	Source of isolate	Number of isolates	Results	Reference, year
DR Congo	September 2010 to May 2011	*Salmonella enterica* serotype Typhi	Isolates were from blood cultures of children from birth to 10 years	118	94% of the strains were resistant to amoxicillin 23% were multidrug resistant and 41% were resistant to ciprofloxacin	Phoba *et al.* (2012)
Mozambique	2005	*Neisseria gonorrhoea*	The strains were isolated from men and women with urethral and vaginal discharge, respectively	270	7% of strains were resistant to kanamycin and 77% were resistant to tetracycline	Apalata *et al.* (2009)
Ethiopia	2006-2012	*Neisseria gonorrhoea*	Men and women with urethral and vaginal discharge, respectively	29	27.8% of strains were resistant to ceftriaxone, 41% were ciprofloxacin resistant; 94% and 92% were resistant to penicillin G and tetracycline, respectively.	Tibebu *et al.* (2013)
South Africa	January 2006 to June 2006	*Escherichia coli*	Isolates were from blood cultures, population not specified	471	84% of isolates were ampicillin resistant, 11, 10 and 6% were resistant to cefuroxime, ceftriaxone and cefipime, respectively; 11, 37 and 20% were resistant to piperacillin-tazobactam, amoxicillin-clavulanate and ciprofloxacin, respectively	Brink *et al.* (2007)
		Klebsiella pneumonia	Isolates were from blood cultures, population not specified	636	98% resistance was observed in ampicillin, 52%, 46% and 44% resistance was seen in cefuroxime, ceftriaxone and Cefepime, respectively; resistance to ciprofloxacin, levofloxacin and ertapenem were 31%, 32% and 2% respectively.	
		Enterobacter spp.	Isolates were from blood cultures, population not specified	244	Resistance to cefepime was 20%. Additionally, 30% and 12% showed resistance to piperacillin/tazobactam and ciprofloxacin respectively.	

Table 2.13 An overview of the resistance patterns of clinically relevant micro-organisms in Africa (continued)

Location	Inception Year	Organism	Source of isolate	Number of isolates	Results	Reference, year
South Africa	January 2006 to June 2006	*Pseudomonas aeruginosa*	Isolates were from blood cultures, population not specified	382	Resistance to meropenem and imipenem were 42 and 45%, respectively. Resistance to cefepime, piperacillin-tazobactam and fluoroquinolones was 53, 48 and 46%, respectively	Brink *et al.* (2007)
		Acinetobacter baumannii	Isolates were from blood cultures, population not specified	190	Isolates resistant to tobramycin were 19%, resistance to meropenem and imipenem are 32 and 33%, respectively. Resistance to ceftazidine and levofloxacin were 43 and 31%, respectively.	
		Staphylococcus aureus	Isolates were from blood cultures, population not specified	629	Resistance to oxacillin was seen in 36% of isolates; 11, 29 and 12% were resistant to rifampicin, trimethoprim/sulphamethoxazole and gentamicin, respectively.	
Mozambique	2001-2005	*Haemophilus influenza*	Isolates were from blood cultures and CSF in children under five years.	106	39% of isolates were resistant to chloramphenicol; strains resistant to ampicillin and co-trimoxazole were 35 and 74%, respectively.	Roca *et al.*(2008)
Mozambique	May 2001 to April 2006	*Streptococcus pneumonia*	Isolates from blood cultures in patients younger than 15 years	1 592	Isolates resistant to ampicillin, co-trimoxazole, erythromycin and penicillin were 11, 44, % and 11%, respectively.	Mandomando *et al.* (2010)
		Staphylococcus aureus			Isolates resistant to ampicillin, co-trimoxazole, erythromycin and penicillin were 90, 31, 35 and 90%, respectively	
		Haemophilus influenza			Resistance to ampicillin and co-trimoxazole was 46 and 77%, respectively.	
		Enterobacter spp.			Resistance to ampicillin and co-trimoxazole was 90 and 20%, respectively.	

Table 2.13 An overview of the resistance patterns of clinically relevant micro-organisms in Africa (continued)

Location	Inception Year	Organism	Source of isolate	Number of isolates	Results	Reference, year
Mozambique	May 2001 to April 2006	*Klebsiella pneumonia*	Isolates from blood cultures in patients younger than 15 years	1 592	All strains were resistant to ampicillin with 70% being resistant to co-trimoxazole	Mandomando *et al.* (2010)
		Pseudomonas aeruginosa			80% of isolates were resistant to ampicillin with 70% resistant to co-trimoxazole	
South Africa	2011	*Klebsiella pneumoniae*	The organism was isolated from urine	1	Incidence of *Klebsiella pneumoniae* carbapenemase (KPC-2)	Brink *et al*. (2011)
		Klebsiella pneumoniae	The strain was isolated from sputum	1	Incidence of New Delhi Metallo-Beta-Lactamase (NDM-1)	

2.3.5 Importance of antimicrobial resistance surveillance

According to Brooks *et al*. (2006:394), Cosgrove and Carmeli (2003:1433), and Masterton (2008:21-22), information on the patterns of resistance in the society or in healthcare institutions is crucial for the following reasons:

- It can help determine the outcome of therapy for individual patients with specific infections.
- The physician and also the hospital can have an upper hand in the use of the appropriate antimicrobial agents and dosing strategies to help reduce resistance.
- It can provide knowledge on good infection and antibiotic control to prevent the emergence of infections caused by resistant strains.
- Important decisions on the type of programmes to fund and track to prevent the spread of antimicrobial resistance can be obtained from information on resistance patterns.

2.3.6 Impact of antimicrobial resistance

The best way of describing the impact of resistance is to take a cursory look at the happenings in the pre-antibiotic era. In the pre-antibiotic era, infections due to micro-organisms were the major causes of morbidity and mortality causing tremendous psychological effects on individuals and families (McKenna, 2013). A simple bruise led to septic shock; ear infections caused deafness; sore throats led to heart failures; five out of every thousand women died during childbirth, one out of nine died of skin infections; and three out of ten people died from pneumonia (McKenna, 2013).

The present-day antibiotic era paints a brighter picture; though infectious diseases are a burden, its prognosis is excellent. Major advances in surgery, organ transplants and cancer chemotherapy owe their success to the discovery and development of antibiotics (Howard *et al*., 2013; Laxminarayan *et al.,* 2013; WHO, 2012:3). Antimicrobial resistance can be linked to the pre-antibiotic era with many medical misadventures.

Presently, resistance to antibiotics causes an increase in morbidity, mortality and medical costs associated with infections (Cohen, 1992:1053; Crowther-Gibson *et al.*, 2011:567; Laxminarayan *et al.,* 2013). The risk of dying as a result of a serious infection caused by a resistant strain is approximately twice that in patients with infections caused by susceptible bacteria (WHO, 2012:3). The prognosis of an infection caused by resistant strains is furthermore poor compared to that caused by susceptible strains. The impact of

antimicrobial resistance is usually assessed from the perspectives of the physician, patients, hospital or healthcare institutions, third-party payers and the pharmaceutical industry (Cosgrove & Carmeli, 2003:1434; McGowan, 2001:286).

The rates of morbidity and mortality increase due to the delay in providing effective therapies for specific infections (Cohen, 1992:1053). These are found in instances where there is resistance to the drug of choice for a specific infection or to the appropriate empiric therapy for a given syndrome. Additionally, the alternate therapies are more costly than the empiric therapy, causing economic disability to families. These alternative therapies are sometimes difficult to administer. The alternate therapy may also be more toxic than the standard therapy, with increased adverse effects (WHO, 2012:3).

A mathematical model was developed by the Canadian Committee on Antimicrobial Resistance (2003:159) to determine the cost of providing care for patients with infections from resistant strains. From their model, there was an estimated additional cost between 14 to 26 million dollars in direct hospitalisation, increased laboratory costs of 10 million dollars, and cost of quarantining carriers of 16 million dollars to the Canadian health sector.

In the European Centre for Disease Prevention and Control (ECDC) technical report on the trends and burden of antimicrobial resistance, the study showed that approximately 25 000 deaths in Europe were as a result of infections from resistant strains, mostly caused by MRSA (ECDC, 2009:13). The cost of extra hospital days was estimated to be 2.5 million euros, extra costs incurred by hospitals were estimated to be 900 million euros, and extra outpatient costs were 10 million euros. Loss of productivity due to absence from work was 150 million euros, and loss of productivity due to death was estimated to be valued at 450 million euros (ECDC, 2009:13).

In the United States, it is estimated that two million infections are caused by resistant strains of microorganisms, which results in 23 000 deaths annually (CDC, 2013:11). There has been a request by the President's budget to allocate $30 million annually for five years to combat antimicrobial resistance alone (CDC, 2013:11). The total cost of antibiotic resistance in the United States is estimated to be $20 billion in excess of direct medical cost (CDC, 2013:11).

In a study by Engemann and his colleagues (2003:586), patients with MRSA surgical site infections were found to be at greater risk of mortality, longer duration of hospitalisation and increased hospital costs, than patients with the same infection caused by methicillin-susceptible *Staphylococcus aureus* (MSSA). Similar studies performed by Cosgrove *et al*.

(2005:171) and Reed *et al.* (2005:182) yielded comparable results. From de Kraker and his colleagues' study (2011:3), involving over 1 200 hospitals from 31 European countries, there were an estimated 8 000 deaths recorded as a result of infections from resistant *Escherichia coli* and MRSA. The extra cost resulting from treatment was estimated to be 62 million euros.

From the studies mentioned above, it is clear that antimicrobial resistance is detrimental to the individual and the society, causing medical, social and economic disadvantages. The biggest threat to resistance is the inadequate funding for the discovery and development of newer antibiotics (Piddock, 2013:1010), and research for newer antibiotics has slowed down. Pharmaceutical companies envisaged a total eradication of infectious diseases and most industries will market endless options for antibiotics. However, this is not the picture now (Laxminayaran *et al*., 2013). The biggest fear of running out of options to treat infection has already arrived as demonstrated by the case in New Zealand (McKenna, 2013).

Knowledge on the implications of resistance serves as a prompter to healthcare providers to support the prevention of resistance; help formulate guidelines to influence appropriate antibiotic prescribing; and also guide policymakers as to which programmes to fund (Cosgrove, 2006:82). Medicine has come far and antimicrobial resistance puts achievements such as organ transplantation, cancer chemotherapy and major surgery at a higher risk (McKenna, 2013).

2.3.7 Measures to control antimicrobial resistance

In 2001, the World Health Organization (2001:4-7) addressed six strategies to combat the spread of resistance globally. These strategies are:

- Reduction in the burden of disease and the spread of infections;
- Improvement of access to appropriate antimicrobials;
- Improvement in the use of antimicrobials;
- Strengthening the health system and the surveillance capacities;
- Enforcement of regulations and enforcements; and
- Encouraging the development of appropriate new drugs and vaccines.

Countries have adopted these strategies; for example, in the United Kingdom, a cross-government antimicrobial strategy has been launched with the above objectives defining the role of the commission (The Infectious Dieases and Blood Policy Team, 2013). In South

Africa, three main strategies *viz*. surveillance activities to monitor antimicrobial resistance, vaccination; and infection prevention and control activities, are present to control antimicrobial resistance (Gelband & Duse, 2011:554)

2.4 Global patterns of antimicrobial use

The WHO describes surveillance of antimicrobial use as the main 'corner stone' of national and international efforts to control antimicrobial resistance (WHO, 2012:13). Monitoring the use of antimicrobials is beneficial for the following reasons (Hans & Ramsamy, 2013:368; WHO, 2012:13):

- It provides vital information for decision-makers on public health issues through the systematic collection and analysis of health-related data.
- Surveillance data provide the information, insight and tools necessary to guide policy and evaluate measures to promote the appropriate use of antibiotics at all levels of healthcare.
- It provides information on how and the quantity of antibiotics used in a setting.
- It is seen as complementary to data on resistance to help inform policy decisions.
- It is a vital tool in identifying priorities for public health interventions and educational campaigns and regulatory measures through the appropriation of resources.

In view of the knowledge that antibiotic use correlates with an increase in resistance, it is prudent to know the pattern of use of antibiotics in society. Knowledge about the pattern of use of antibiotics is crucial for the development of interventions aimed at promoting rational use (Wirtz *et al.,* 2010:219). The subsequent paragraphs provide an overview of studies performed to measure antibiotic use globally.

2.4.1 Patterns of antibiotic use in Europe

Antibiotic use in Europe has seen proper documentation over the past decade with several studies from the European Surveillance of Antimicrobial Consumption (ESAC) and the European Study Group on Antibiotic Policies (ESGAP). Iconic studies conducted to measure antibiotic use in European countries are discussed in the subsequent paragraphs.

The use of antibiotics in 54 Dutch hospitals from 1991 to 1996 was investigated by Janknegt *et al*. (2000:252). They reported an increase in all pharmacological groups of antibiotics throughout the study period. Penicillins were the most widely used antibiotics, with

amoxicillin/clavulanate dominating. The use of quinolones also saw a steady increase, with ciprofloxacin and norfloxacin being dominant.

In Gould's study analysing antibiotic use in 140 European hospitals, the penicillins, fluoroquinolones and cephalosporins were the most commonly used antibiotics during the study period. The study, however, did not explore the reasons for use (Gould, 2005:122).

Cars *et al*.'s (2001:1853) study, involving 15 European countries in 1997, revealed that half of the countries showed a minimum of 4% increase in antibiotic use. However, a notable increase was seen in Italy and Luxembourg; 34% and 12%, respectively. A reduction in antibiotic use was found in five of the countries, with Sweden leading and Greece showing the least (Cars *et al*., 2001:1854). The most commonly used antibiotics were the broad-spectrum penicillins, tetracyclines and macrolides. Fluoroquinolones were the most used antibiotic in Portugal. Cars *et al.* attributed the variations in use to the differences in the prevalence of bacterial infections, physicians and patients' attitudes to antibiotics, historical backgrounds, cultural and social factors, and variations in healthcare systems (Cars *et al.*, 2001:1853-1854).

Ferech *et al.* (2006:403-404) analysed outpatient antibiotic use in Europe from 1997 to 2003, and revealed an increase in use for most of the European countries, especially in France and Greece. However, notable reductions in antibiotic use were seen in countries such as Belgium. In all 25 participating countries, penicillins were the most widely prescribed antibiotic, followed by the fluoroquinolones. The use of other antibiotics, such as the macrolides and tetracycline, remained constant during the study period. Ferech *et al*. explained that variations in antibiotic use among the European countries were due to differences in the incidence of community-acquired infections, culture, healthcare structures, knowledge about antimicrobials, pharmaceutical market and regulatory practices.

Goossens *et al.* (2005:581-583) in their study from 1997 to 2002, also observed lower antibiotic use in northern Europe and relatively higher consumption in the south. They noted the growing use of newer antibiotics such as the macrolides, amoxicillin/clavulanic acid and the quinolones, though the penicillins and the first-generation cephalosporins were the most widely prescribed. Antibiotics were mostly prescribed by health practitioners in the south as they labelled most respiratory tract infections as bronchitis, unlike those in the north, who regarded these infections as either a common cold or influenza.

Adriaenssens *et al*. (2011a:6-7) confirmed the trend from Goossens *et al*. in 33 European

countries between 1997 and 2009. Greece showed the highest use of antibiotics as compared to Cars *et al.'s* investigations in 1997, where Greece showed a decrease in antibiotic use. Penicillins were the most widely used across all the countries and the use of fluoroquinolones, especially the newer compounds, was seen to have a proportional increase. Striking geographical variations have been observed across the European countries, where narrow spectrum penicillins and the first generation cephalosporins are mostly prescribed in the Nordic countries, compared to the southern European countries where there is an increase in the use of amoxicillin/clavulanic acid.

In 2007, Dumartin *et al*. (2010:2030) analysed antibiotic usage patterns involving 530 hospitals (teaching and non-teaching, cancer and rehabilitation centres). The penicillins were the most widely used antibiotics in all centres. Fluoroquinolones was the second most widely used, especially in the rehabilitation and cancer centres. These centres were also observed to have the highest use of glycopeptides and carbapenems.

2.4.1.1 Patterns of fluoroquinolone use in Europe

In the Netherlands, fluoroquinolones accounted for 6% of total antibiotic use in 1994 (Natsch *et al.*, 1998:23). The highest use of fluoroquinolones was recorded in patients above 75 years and was mostly used in the haematology and oncology wards, possibly for prophylaxis in neutropenic patients (Natsch *et al.*, 1998:23). The study, however, did not explore the use of the sub-pharmacological groups of fluoroquinolones.

The analysis of fluoroquinolone use in 2003 by Ferech *et al*. (2006:424) showed that the use of first-generation fluoroquinolones (mostly norfloxacin) formed 85% of fluoroquinolone prescriptions in Croatia and approximately 40% in the Czech Republic, Sweden, France and Slovenia. Cinoxacin was mainly used in Italy, flumequine in France, oxolinic acid in the Czech Republic, Poland and Slovakia, piromidic acid in Italy, and rosoxacin in Portugal. The second-generation fluoroquinolones were the most commonly used in Europe and exceeded more than half of total fluoroquinolone use in all countries, except Croatia. Ciprofloxacin alone constituted approximately 40% of total quinolone use in all countries. The use of ofloxacin was very common in Israel and Slovakia, while levofloxacin use was dominant in Italy. Among the third-generation quinolones, only gatifloxacin and moxifloxacin were prescribed in Europe and their use was recorded in all except six countries. Moxifloxacin represented the largest proportion of the third-generation fluoroquinolones. Gatifloxacin use was only found in Germany.

Adriaessens *et al.* (2011b:6-7) performed a similar study assessing fluoroquinolone use from 1997 to 2007 in 33 European countries. From their study, there was a striking variation in outpatient prescribing, with Italy emerging as the country with the highest use of quinolones (levofloxacin being dominant). Belgium showed the highest third-generation fluoroquinolone use (mainly moxifloxacin). The use of fluoroquinolones was dominant in southern Europe, followed by Eastern Europe, and lowest in Northern Europe. The use of the second-generation quinolones saw a steady increase, with a decrease in the use of the first-generation quinolones in most countries. In countries such as Belgium, Luxembourg and Portugal, for example, levofloxacin and moxifloxacin were prescribed in large quantities during the winter periods. This trend was quite unclear owing to the fact that quinolones are not first-line treatment for lower respiratory tract in ambulatory care in most European countries. Older quinolones, such as norfloxacin and ofloxacin, were still being highly prescribed in countries such as Croatia, but there was a decreasing trend in consumption in most of the countries. Ciprofloxacin was still the most widely prescribed quinolone in clinical practice and its consumption increased in many countries from 1997 to 2009. Adriaessens *et al*. (2011b:6-7) suggested that the use of ciprofloxacin was probably heightened by the expiration of the patent in 2003, which was followed by the introduction of generic brands. The use of fluoroquinolones for the treatment of urinary tract infection was also increased during the winter months, e.g. ciprofloxacin in Slovakia, Poland, Hungary, Latvia and the Russian Federation.

2.4.2. Patterns of antibiotic use in America

Loeb *et al.* (2001:378) determined antibiotic use in facilities providing chronic care in Canada from November 1996 to October 1997. Their study showed amoxicillin and ciprofloxacin being the most commonly used antibiotics during the study. These antibiotics were mostly prescribed for lower respiratory tract infections and urinary tract infections. Other antibiotics, such as trimethoprim and the cephalosporins, were also used for the treatment of urinary tract infections and soft tissue infection.

Raveh *et al.* (2001:142) conducted a study at a medical centre in the United States for the elderly in 1998, showing that cephalosporins (cefuroxime and cefazolin) are the most prescribed and used antibiotics. This was followed by ampicillin in combination with gentamicin, amoxicillin/clavulanate and ciprofloxacin. The common diagnoses were respiratory tract infections, urinary tract infections, sepsis, intra-abdominal infections and soft tissue infection.

From the study by Goossens *et al*. (2007:1093), antibiotic use in the United States is generally higher than in most European countries, with a higher preference in the use of newer antibiotics. Tetracyclines, macrolides and fluoroquinolones were the most widely used antibiotics in outpatients in the United States, contrary to consumption in Europe, where penicillins were the most frequently used antibiotics during the study period. First-line treatments for lower respiratory tract infection are the fluoroquinolones, doxycycline and the macrolides. According to Goossens *et al*. (2007:1093), these differences can be attributed to variations in treatment guidelines, health systems and marketing policies, e.g. the United States has no all-inclusive national health plan, and there are essentially no deterrents to prescribing any given outpatient antibiotic, other than the patient's willingness to pay.

In South America, the increase in use of antibiotics is similar to the situation in Europe and the United States. Wirtz and his colleagues' (2010:220-222) study from 1997 to 2007 revealed an increase in use of antibiotics in Peru, Venezuela, Uruguay and Brazil, with penicillins and quinolones being the most widely used antibiotics. However, in Mexico and Colombia, antibiotic use decreased. The use of quinolones, especially ciprofloxacin, increased throughout the study period, especially in Venezuela and Argentina. The increase in macrolide, lincosamides and streptogramin use was greatest in Peru, followed by Brazil, Argentina and Chile (Wirtz *et al*., 2010:220). The study could not associate the variation in use to potential causes, but pointed out that the inappropriate prescribing by physicians, public demand for antibiotics, the purchase of antibiotics without prescriptions and a lack of regulations may have affected the trends in antibiotic use.

2.4.2.1 Patterns of fluoroquinolone use in America

In a study conducted by Polk *et al*. (2004:499) analysing the trends in fluoroquinolone use in 24 hospitals from 1999 to 2001, there was an estimated increase in total use by 15%. There was an observed seasonal increase in total fluoroquinolone use during the fourth quarter of each year and the subsequent first quarter of the following year. Levofloxacin was the most commonly prescribed fluoroquinolone and its use increased from 64 to 82% of total fluoroquinolone use. The use of ciprofloxacin decreased during the study period, but was considered to be statistically insignificant (Polk *et al*., 2004:499). However, the use of fluoroquinolones at the community level recorded ciprofloxacin being the most prescribed until the first quarter of 2001. The introduction of newer fluoroquinolones, such as gatifloxacin and moxifloxacin, contributed to the overall increase in fluoroquinolone use (Polk *et al*., 2004:499).

In Goossens *et al.'s* (2007:1094) study in 2004, fluoroquinolones accounted for less than 1% of total antibiotic use in the United States. Levofloxacin was the most prescribed fluoroquinolone, followed by moxifloxacin. Goossens and colleagues' study confirms Polk *et al.'s* (2004:499) study with respect to levofloxacin being the most used fluoroquinolone in the United States.

According to Wirtz *et al*. (2010:221), fluoroquinolone utilisation has increased in most countries in South America, with ciprofloxacin being the most widely prescribed. The use of newer drugs, such as levofloxacin, was highest in Venezuela, whereas moxifloxacin was the most widely used quinolone in Mexico.

2.4.3 Patterns of antibiotic use in Asia

A year-long study by Kotwani and Holloway (2011:5-6) in New Delhi, India, revealed that penicillins were the most commonly used antibiotics, followed by fluoroquinolones, macrolides and cephalosporins. The use of the various antibiotics remained relatively constant during the study period (December 2007 to November 2008). However, fluoroquinolone use increased during the rainy seasons. This was attributed to the incidence of diarrhoeal diseases during the rainy seasons.

2.4.4 Patterns of antibiotic use in Africa

A study by van den Boogaard *et al*. (2010:146) involving 14 pharmacies from February to March 2009 in Tanzania determining the sale of antibiotics showed penicillins being the most widely used antibiotic. This was followed by the fluoroquinolones, macrolides, tetracycline and sulphonamides and trimethoprim. Their study did not ascertain the reasons for use.

According to Abula and Kedir (2004:36), analysing the usage patterns of antibiotics in patients in a surgical ward at a teaching hospital in Ethiopia; ampicillin was the most widely used antibiotic, forming approximately 40% of antibiotics dispensed. Ampicillin was mostly used combined with chloramphenicol and metronidazole for pre-operative prophylaxis and the treatment of infections.

In South Africa, antibiotic consumption in the private sector is derived from the Institute of Medical Statistics (IMS) with data collected from wholesalers and direct sales from manufacturers to pharmacies (Essack *et al*., 2011:565). The report, however, does not measure antibiotic use according to the daily defined dose (DDD), as recommended,

causing a major challenge for meaningful comparison with the public health sector and other countries. From the data from IMS, there has been an increment in the use of antibiotics by approximately 6.5% from 2009 and 2010 with broad spectrum penicillins being the most widely used, and the fluoroquinolones among the top five antibiotics (Essack *et al.*, 2011:565-566).

A study analysing antibiotic use from nine randomly selected primary healthcare clinics in the South African private healthcare sector revealed that penicillins (amoxicillin) and the sulphonamides (co-trimoxazole) were the most widely used antibiotics, especially for the treatment of upper respiratory infections (Katende-Kyenda *et al.,* 2006:704).

2.4.4.1 Fluoroquinolone use in Africa

In van den Boogaard and colleagues' study (2010:146), fluoroquinolones formed 13% of antibiotic sales in Moshi, a town in Tanzania, from February to March 2009. Ciprofloxacin formed 74% of total fluoroquinolone use, followed by norfloxacin and levofloxacin less than 1% of total fluoroquinolone sales. The study, however, did not address the indication for use.

There is little information on the pattern of fluoroquinolone use in South Africa. According to IMS data, the most frequently used fluoroquinolones are levofloxacin (Tavanic®), moxifloxacin (Avelon®) and ciprofloxacin (Ciprobay®). These three fluoroquinolones were part of the top twenty antibiotics in terms of market share in 2009 and 2010 in the private sector (Essack *et al.*, 2011:566). There is, however, little knowledge on the pattern of use of fluoroquinolones in the country (Essack *et al.,* 2011:566).

From these notable studies, the use of antibiotics has seen an increase globally. The dominant use of penicillins (especially in combination with a beta-lactamase inhibitor) is observed in most of these studies. Ciprofloxacin appears to be the most widely prescribed fluoroquinolone globally.

2.4.5 Irrational use of antibiotics

Detailed knowledge of antibiotic use is necessary for the following reasons (WHO, 2013:25):

- to implement national strategies for judicious antibiotic use;
- to provide solutions to the threat posed by resistant micro-organisms;
- to provide information as a first step in creating awareness of the careful use of

antibiotics to prescribers and policymakers. This will help define levels of appropriate use in an institution; and

- to be used as an assessment for testing the effectiveness of interventions introduced to optimise the use of antibiotics in a healthcare facility.

Diseases of microbial origin are major causes of morbidity and mortality in the world, especially in developing countries (Mukonzo *et al*., 2013:308). In South Africa, infections form a significant proportion of the burden of disease, with human immune-deficiency virus/acquired immune deficiency syndrome (HIV/AIDS) being the major cause of mortality (Crowther-Gibson *et al.,* 2011:567).

It is estimated that 50% of patients who visit healthcare facilities globally are prescribed with at least one antimicrobial agent – of which a significant proportion is inappropriate (Abula & Kedir, 2004:37; Al-Ghamdi *et al*., 2002:118; Gonzales *et al.,* 2001:759; Katende-Kyenda *et al.,* 2006:705; Polk *et al*., 2007:671; Raveh *et al.*, 2001:146; Tunger *et al*., 2000:134). Several antibiotics, especially penicillins, macrolides and quinolones, are used incorrectly in the treatment of presumed respiratory tract infections (Katende-Kyenda *et al.*, 2006:705; Wolff, 1993:347).

In some African countries, such as Nigeria, antibiotics are readily available in hospitals, pharmacies, licensed medical stalls and drug stores, road side sellers and hawkers (Enato & Uwaga, 2011:41). Unfortunately, they are dispensed without a prescription (Enato & Uwaga, 2011:41). In South Africa, in particular, the misuse of antibiotics is more common in the private sector than the public sector because of the availability of drugs, physicians being allowed to prescribe outside the standard treatment guidelines and the higher demand for antibiotics (Essack *et al.,* 2011:564). The widespread availability and irrational use have a direct influence on the emergence of antimicrobial resistance. The inappropriate use of antimicrobials by an individual causes selection-resistant organisms that spread in the community (WHO, 2012:32).

Rational drug use is defined by the WHO (2012:33), as *patients receiving medication appropriate to their clinical needs in doses that meet their own individual requirement for an adequate period of time and the lowest cost to them and the community*. Gaur and English (2006:343) also define the judicious use of antimicrobials *as the usage of the drug only when indicated, choosing a cost-effective agent which provide the appropriate coverage for the diagnoses that is suspected and prescribing the optimal dose and duration of the antimicrobial agent*. From these two definitions, the diagnoses, choice of antimicrobial agent,

duration of therapy, dose and cost-effectiveness of the antimicrobial agent are of prime importance in deciding what constitutes the prudent use of a drug. The opposite is also true – irrational drug use constitutes over-prescribing, under-prescribing, dispensing unnecessarily, and use without justification (WHO, 2012:33).

According to Radyowijati and Haak (2002:8), the prescribing and the community use of antimicrobials are directly influenced by an amalgamation of medical, psychosocial, cultural, geographical and political factors. Blommaert *et al*. (2014:544) pointed out factors such as seasonal variations, healthcare expenditure on gross domestic income, aged population, and the availability of standard treatment guidelines in health institutions correlating with high antibiotic use in a population. Conversely, restrictions of marketing activities towards prescribing, low population density, high educational attainment and some degree of atheism are associated with lower use of antibiotics. The afore-mentioned factors fall under the three main determinants of antimicrobial use, namely the prescriber, the dispenser and the patient or the community. These likely determinants of antibiotic use are addressed in the subsequent paragraphs.

2.4.5.1 Determinants of antibiotic prescribing

The concept of rational drug prescribing entails prescribers following a standard process of prescribing in conformity with the formulary or standard treatment guidelines of the institution (Chukwuani *et al*., 2002:180). Radyowijati and Haak (2003:741), Chukwuani *et al.* (2002:189-194), Adorka *et al*. (2013:347), and Gaur and English (2006:344), from their studies, outlined the following factors influencing the prescribing patterns of physicians:

- **Years of practice experience**

Chukwuani *et al*. (2002:184) noted that prescribers with more than ten years of experience mostly prescribed antibiotics empirically. According to Duse (2005:39), physicians are often of the view that most illnesses have a bacterial aetiology and tend to treat patients empirically. Appropriate prescribing patterns have been observed mostly in trainee physicians than in permanent staff; and in non-teaching hospitals than in teaching hospitals. Guar and English (2006:345) explained that trainees may be more acquainted with the most recent advances in antimicrobial chemotherapy and follow guidelines more readily.

- **Time spent with the patient in the consulting room**

It has been hypothesised that physicians tend to prescribe antibiotics when they have shorter contact times with patients. Adorka *et al.* (2013:348) revealed that prescribers' workload was directly related to inappropriate prescribing. Physicians, in a hurry to see all patients, may not have patience to properly diagnose, subsequently resorting to the use of antibiotics (which are mostly not indicated).

- **Patient demand and expectations for antibiotics**

Prescribers fear that when they do not prescribe antibiotics for their patients they might lose them to others who will. Britten and Ukoumunne (1997:1509), conducting a survey in London, showed that patients' expectations influence general practitioners' prescribing in that patients' hopes of receiving a prescription mostly far exceed both the prescribers' perceptions and the level of prescribing. However, in studies performed by Adorka *et al.* (2013:347) and Huebner *et al.* (2003:506), prescribers in Lesotho and South Africa, respectively, reported they were not influenced by patients' expectation to receive an antibiotic.

- **Inadequate information on the use of antibiotics among prescribers**

The term 'prescriber' does not only refer to physicians, but a host of other healthcare providers who are in the position to issue drugs in a defined setting with variable clinical backgrounds, e.g. nurses, pharmacists and physician assistants, including those with no medical background (Gaur & English, 2006:346). Irrational prescribing is common in prescribers with little clinical background. Additionally, among those with clinical background, medical representatives and commercially-oriented medical publications are their main sources of information (Huebner *et al.,* 2003:506).

- **Economic factors, e.g. economic incentives**

In some instances, prescribers make gains by prescribing or even recommending certain antibiotics (newer and expensive) for the drug manufacturer in the form of incentives. In most of the cases, these antimicrobials are not clinically indicated (Gaur & English, 2006:92).

- **Inadequate and untimely laboratory results**

Most physicians prescribe empirically, because few healthcare centres are equipped with laboratories and even when they do, the results are sometimes unreliable (Adorka *et al*., 2013:349; Chukwuani *et al.*, 2002:190). Based on a Ugandan study by Mukonzo *et al*. (2013:308), less than half of the study population's diagnoses were confirmed with laboratory findings. Reasons cited for the empiric treatment of patients included a large time lapse between the request and the results of a laboratory finding, and the costs associated with laboratory services patients were expected to pay.

- **Unstable antibiotic supply**

According to Chukwuani *et al.* (2002:190), prescriber-attributed irrational prescribing is sometimes caused by the unavailability of drugs in the hospital. Physicians have a higher tendency to prescribe according to what is available than what will be most suitable for the patient.

- **Fear of bad clinical outcome**

The study by Adorka *et al.* (2013:348) describing the perception and attitudes of antibiotic prescribing by healthcare providers in public institutions in Lesotho, confirms Huebner and his colleagues' work that approximately half of the physicians prescribe antibiotics with unclear diagnoses or to prevent an infection even when bacterial infections are ruled out. Antibiotics are sometimes used by physicians as a diagnostic tool to determine the nature of a disease. Further investigations are then performed when the patient does not recover from initial treatment.

2.4.5.2 Determinants of antibiotic dispensing and sales

The delivery systems of antibiotics are varied in most countries, ranging from hospitals, pharmacies, private dispensing pharmacies, and licenced chemical sellers with all types of clients drawn to each sector.

Pharmacists are recognised custodians of medications and are also mandated to manage and supervise pharmacies. The central role of the pharmacist is to educate and advise patients on the correct use of medicines. The pharmacist is therefore required to play an

important role in the rational use of antibiotics (Essack *et al*., 2011:564). In some communities, the pharmacist is referred to as a 'doctor' due to his/her immense medical knowledge. Pharmacists may dispense 5% greater or lesser quantities of prescribed antibiotics. This freedom may have a direct influence on the dispensing patterns by pharmacists (Essack *et al*., 2011:564). In some settings, dispensing technicians, pharmacy attendants and even nurses are referred to as 'pharmacists' as they are seen working in the pharmacy with some level of medical knowledge.

According to Radyowijati and Haak (2002:19), patients prefer to purchase drugs directly from pharmacies, instead of seeing the physicians because:

- there appears to be more 'pharmacists' than doctors in most countries;
- the medicines are cheaper to purchase and there is no payment of consultation fees;
- the community has a closer social and cultural relationship with pharmacy attendants; and
- visiting the pharmacy is less time consuming than visiting the hospital.

Factors such as economic incentives, patient demand, inadequate knowledge by dispensers, influence from the pharmaceutical industry and a lack of regulations and enforcements influence irrational dispensing (Radyowijati & Haak, 2003:741).

- **Economic incentives and client demand**

Radyowijati and Haak (2003:741) conducted a review of literature on the determinants of antibiotic use in low-income countries, and found that pharmacists are prepared to meet patients' demands by dispensing the quantity of antibiotics they can afford for the fear of losing their profits, as patients may go elsewhere to purchase them. Additionally, most pharmacies dispense antibiotics for ailments that do not warrant the use of antibiotics to make extra profits. Pharmacists' dispensing patterns are also influenced by pressure from their suppliers who readily give incentives or commissions. Plachouras *et al*. (2010:2-3), from their survey in Greece, showed that 53% of pharmacists from the study population dispensed ciprofloxacin without prescriptions. Surprisingly, all pharmacists in the study population dispensed amoxicillin/clavulanate as over-the-counter medications. These antibiotics were sold without any comments made by the pharmacists or requests for justification of use.

- **Lack of knowledge**

In most African countries, pharmacists are not the only recognised dispensers. Pharmacy technicians, pharmacy interns, pharmacy attendants – all with varied medical backgrounds – are involved in the dispensing process (Radyowijati & Haak, 2003:741). Additionally, the role of the pharmacist is limited to administrative work rather than consultative work; relegating dispensing of drugs to the technicians and assistants. This affects the pharmacist's inability to influence what is being dispensed in the facility. Knowledge on recent developments in antimicrobial chemotherapy may be lacking, affecting the rational use of antibiotics (Goel *et al.,* 1996:1155).

- **Lack of regulation and enforcement**

Against the regulations of the profession, most antibiotics are routinely dispensed without prescriptions. Mukonzo *et al.* (2013:308), from their study in Uganda, pointed out that although regulations exist for the prohibition of the sale of antibiotics without prescriptions, approximately 41% of the total antibiotics dispensed in their study were over-the-counter.

2.4.5.3 Determinants of patient use of antibiotics

The use of antibiotics in communities is strongly influenced by cultural preferences and beliefs. Most patients believe that antibiotics are very powerful drugs capable of treating and preventing all kinds of ailments (Radyowijati & Haak, 2003:741). There is also the perception that taking antibiotics for long periods is harmful, and therefore not necessary to take the full course of therapy. Ultimately, the subject of self-medication is seen to be a major driver of irrational antibiotic use.

Self-medication is defined by the WHO (1998:3) as the selection of medicines by individuals to treat self-recognised illnesses or symptoms. The main drivers of self-medication are the purchasing of antibiotics without prescriptions, and the storage of unfinished or left-over medication for future use (Chukwuani *et al.*, 2002:192; Radyowijati & Haak, 2003:741). Currently, many antibiotics are purchased online *via* the Internet, making it quite impossible to address the issue of self-medication (Plachouras *et al*., 2010:3).

It is common to find patients purchasing a part of an antimicrobial therapy in most developing countries due to financial restraint since most pay out-of-pocket (Gaur & English, 2006:347, Mukonzo *et al.,* 2013:308). In a study by Awad *et al.* (2005:327), 74% of the

respondents from a study conducted in Sudan confirmed the use of an antibiotic without a prescription. In Nigeria, Sakpota *et al*. (2010:6) noted the unwarranted use of ampicillin by university students to manage menstrual cramps was as a result of purchasing the medications without prescriptions. Radyowijati and Haak (2003:741) explained that communities have their own way of using antibiotics upon the advice given by friends and families, and past similar experience with an illness for which a particular antibiotic was given. It has been hypothesised that the persistent prescribing patterns of physicians also strongly influence self-medication by the community. Abasaeed *et al.* (2013:1051), in their study in Abu Dhabi, noted that Co-amoxiclav® (i.e. amoxicillin/clavulanic acid as potassium clavulanate combination) was the most widely prescribed antibiotic by doctors for upper respiratory tract infections and the most widely purchased antibiotic without prescription for cough.

Due to financial restraints, pharmacies are often the first call for medical assistance for most communities. There is the avoidance of the extra charge for consultation and laboratory investigations (Enato & Uwaga, 2011:41). Abasaeed *et al*. (2013:1051), in their study, revealed that 95% of pharmacists dispense antibiotics to persistent patients without prescriptions.

2.4.6. Consequences of irrational antibiotic use

Health consequences of inappropriate antibiotic use (Le Grand *et al*., 1999:91) include:

- Adverse effects leading to morbidity and mortality due to irrational use of antibiotics;
- Limited efficacy especially in taking sub-therapeutic doses of antibiotics;
- Antibiotic resistance resulting from increased use of antibiotics as well as their use in under-therapeutic dosage;
- Drug dependence; and
- Risk of infection from resistant strains of micro-organisms.

According to Pechere (2001:172) and Laxminyaran *et al*. (2013), antimicrobial resistance is a result of natural selection endowing micro-organisms with some level of inherent resistance. Studies have shown that the existence of resistant strains predates the use of antibiotics. For example, Austin *et al.* (1999:1156), in their study, proved that the strength of the selective pressure, i.e. the rate of drug consumption, is intimately and positively associated with the rate of evolution of resistance. Penicillin-resistant *Staphylococcus aureus* was identified in 1940 soon after penicillin was discovered and was administered to

only a few patients. The introduction of tetracycline in the 1950s saw the emergence of resistance in *Shigella* species; erythromycin arrived on the scene in 1953, and erythromycin-resistant *Streptococcus pneumonia* appeared in 1968. The introduction of methicillin met its resistance two years later (Neu, 1992:1065). Levofloxacin, a synthetic antibiotic introduced in 1996, saw resistance in the same year. The story is no different for antibiotics such as linezolid and daptomycin (McKenna, 2013). Studies from Laxminayaran and Brown (2001:189), Turnidge and Christansens (2005:548), Chen *et al*. (1999:234), and Goossens *et al.* (2005:586) confirmed Austin and colleagues' postulation. For most antibiotic-micro-organism combinations, an increase in the consumption of a specific antibiotic or antibiotic class is followed by an increase in resistance to the antibiotic or antibiotic class with a delay of less than six months. Similarly, a decrease in consumption is generally followed by a decrease in resistance (Monnet & Lopez, 2005:127).

Van de Sande-Bruinsma *et al*. (2008:1726) demonstrated the correlation between antimicrobial use and resistance in Europe. They observed that the variation of consumption coincides with the occurrence of resistance at country level. There was a high degree of consistency between penicillin use and penicillin non-susceptibility in pneumococci, as well as for fluoroquinolone use and an increase in fluoroquinolone resistance in *Escherichia coli.*

Hseuh *et al.* (2005:466) confirmed the work of Van de Sande-Bruinsma *et al*. (2008:1726) in a 13-year study in a Taiwanese teaching hospital. In their study, Hseuh *et al.* (2005) observed cross-resistance, where the widespread use of cefepime, ciprofloxacin and carbapenems was significantly associated with the increase in cefotaxime and ciprofloxacin resistance in *Escherichia coli* and carbapenem resistance in *Pseudomonas aeruginosa,* respectively. An increase in the use of extended-spectrum cephalosporins was also significantly related to the increased incidence of cefotaxime resistance in *Klebsiella pneumoniae*. The increased use of fluoroquinolones was also significantly associated with the increased incidence of cefotaxime resistance in *Klebsiella pneumoniae* and carbapenem resistance in *P. aeruginosa.*

Resistance is an inevitable end that bacteria will sooner or later develop; however, its misuse has been found to be a catalyst, speeding up the entire reaction process.

2.5 Measures to control the use of antibiotics

It is of no doubt that the use of antibiotics has greatly improved human life and consequently specific measures need to be employed to guard these drugs judiciously. Assessing the

strategies developed by the World Health Organization in 2001 for the prevention and control of antibiotic resistance (WHO, 2001:4-7), two complementary approaches sum it up, namely: infection control measures to curb the spread of MDR organisms, and improving antibiotic use for the treatment and prophylaxis of infections (Houvinen & Cars, 1998:613).

In view of the evidence that usage is the main driver of resistance, it is logical to reduce resistance by reducing usage (Garcia-Rey *et al*., 2002:162; Livermore, 2005:451; Smith & Coast, 2002:126). Although the overuse of antibiotics can cause the emergence of resistance, appropriate changes in antibiotic use can lead to retrieval of susceptibility (Yates, 1999:25). Theoretically, any measure that optimises antimicrobial use has an effect on the emergence and spread of resistance through changes in antibiotic selective pressure. Several strategies have been adopted to influence the use of antibiotics to improve health outcomes, namely: ensuring cost-effective therapy, reducing adverse health and ecological effects, and ultimately reducing drug resistance (Allerberger *et al*., 2009:1175). Although a reduction in the use of antimicrobials may not be immediately followed by a reduction in resistance, the controlled use of antimicrobials is still of prime importance (Gaur & English, 2006:344).

The greatest success in optimising antimicrobial use has been seen with programmes that use several strategies targeting antibiotic decision-making at several different points (Dunagan & Medoff, 1992:266; Finch *et al.*, 2004:44; Houvinen & Cars, 1998:613; Vlahoric-Palcekski *et al*., 2000:101). According to Davey *et al.* (2013:6), interventions to optimise antimicrobial use can be grouped as follows: restrictive or coercive, persuasive or educational and structural interventions. A discussion on these interventions follows in subsequent paragraphs.

2.5.1 Restrictive interventions

Davey *et al.* (2013:6) explained restrictive interventions as those aimed at limiting the prescribers' freedom to a selection of specified antibiotics. This involves the distribution of learning materials, informative meetings, local consensus processes, educational outreach visits, local opinion leaders, reminders given verbally, on paper or on computer, audits and feedback.

Restrictive interventions to improve antibiotic use have been found to have more success rates than educational interventions (Brown, 2006:164). Ozkurt *et al*. (2005:399-340) found a 70% decrease in the use of antibiotics and an 18% decrease in expenditure after the

implementation of a restriction policy. Basseti *et al*. (2001:534) and Erbay *et al.* (2003:311) both agreed to the pronounced positive effects that the use of restrictive interventions has on the overall susceptibilities of organisms, appropriate prescribing, improved patient outcomes and reduced expenditure on antibiotics. Brown (2006:166) recommends enforcement by health professionals, especially pharmacists, with the use of restrictive measures to ensure the prudent use of antimicrobials. This is because the introduction of these measures may cause adversarial relationships between prescribers (who may perceive this to be dictatorial) and other health professionals. Examples of restrictive interventions that have been proven to be effective include:

- **Antibiotic formulary restriction:** Formulary guidelines are effective means of controlling antibiotic use by reducing variations in the method and standard of care (Brown, 2005:165; Dunagan & Medoff, 1992:266; Fishman, 2006:59-60; Yates, 1999:26).
- **Prior approval programmes:** Justification of use approaches have been designed to optimise antibiotic use. These may include prior approval by an infectious disease specialist, antibiotic order forms and automatic stop orders that require validation for the use of the antibiotics (Weistein, 2001:190; White *et al*., 1997:231).
- **Antibiotic cycling:** Cycling or rotation is the programmed replacement of a class of antibiotics with a different class having a similar spectrum of activity. These substitutions may be followed by any number of substitutions, but the cycle must be repeated, with a re-introduction of the original class/drug to introduce heterogeneity in the use of antibiotics (Merz *et al*., 2004:2864). This allows resistance rates to the withdrawn drug to stabilise, or even decrease, during the period of restriction and enabling it to be re-introduced at a later date with its efficacy intact (Brown & Nathwani, 2005:6; Kollef, 2006:86; Masterton, 2005:4).

2.5.2 Educational or persuasive interventions

Persuasive interventions are said to complement the overall effect of other interventions. The most effective form of education is individual instruction by an infectious disease expert given at the time of antibiotic choice. Additionally, education must be a continuous effort; if not, results are diminished over time (Brown, 2005:163). Education-based interventions are most effective when the prescribing physician and dispenser see it as help rather than being authoritative. Natsch (2005:125) believed the best approach is to provide real-time feedback and educated suggestions and then to allow the physician to make the final choice based on this information.

Advantages of the educational approach include reduced red tape, less conflict, a greater variety in antibiotics prescribed, and the direct involvement of infection control specialists and microbiologists (Brown, 2005:164). Additionally, the inclusion of physicians as contributors in the implementation of improved antibiotic utilisation procedures results in increased compliance. Educational interventions that have shown to be successful include audit and feedback, computer-assisted decision support, educational outreach, mass media and printed educational materials (Natsch, 2005:125).

2.5.3 Structural interventions

Structural interventions include the changing from paper to computerised records, prompt laboratory testing, computerised decision support systems and the introduction of organisations for quality monitoring mechanisms (Davey *et al.,* 2013:6). The subsequent paragraphs outline two major interventions developed to curb the use of antimicrobials.

- **Laboratory controls**

The medical laboratory in the healthcare facility can help in the prudent use of antimicrobials by providing clinical interpretation to laboratory reports; performing selective susceptibility testing that includes antimicrobials listed in the hospital formulary; and reporting trends and susceptibility patterns can be collected to guide optimal empirical therapy (Brown, 2006:170).

- **Antibiotic stewardship programmes**

Antimicrobial stewardship, defined by Gerding (2001:403), and agreed by Fishman (2006:55), is *the optimal selection, dosage, and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance*. Antimicrobial stewardship is a key element of a multidimensional approach in the prevention of the emergence of antimicrobial resistance. Optimising antimicrobial use by minimising exposure to drugs, adjusting dosage, reducing obsolete therapies, and targeting therapies to the appropriate organisms are seen as strategies to enhance patients' safety as well as decrease resistance. Practically, prescribing antimicrobial therapy only when it is of benefit to the patient, targeting therapy to the right pathogens, and using the suitable drug, dose and duration.

According to Allerberger *et al*. (2009:1177), the objectives of an antibiotic stewardship programme are to:

- ensure patients get effective, safe and cost-effective antibiotic treatment and prophylaxis;
- prevent and control antimicrobial resistance by promoting its judicious use; and
- reduce the incidence of difficult-to-treat infections caused by multi-drug resistant strains.

Statutory bodies, e.g. European Surveillance on Antibiotic Consumption (ESAC), British Society for Antimicrobial Chemotherapy (BSAC), The Antibiotic Smart Use Program in Thailand, Chennai Declaration in India, European Study Group on Antibiotic Policies (ESGAP), and Global Antibiotic Resistance Partnership (GARP) in South Africa all aim at promoting the objectives of antibiotic stewardship programme. The month of November has furthermore been slated to raise awareness on antimicrobial resistance and the careful use of antimicrobial agents in communities and hospitals in Europe, Canada, The United States and Australia (Earnshaw *et al*., 2013:1003). The use of social media, conferences, communication materials, and media is employed to educate the society on the prudent use of antimicrobial agents.

In South Africa, the "Best Care….Always" campaign, supported by the Federation of Infectious Diseases Societies of South Africa (FIDSSA), the Global Antimicrobial Resistance Partnership (GARP) and the World Health Organization's Alliance for Patient Safety, was launched in 2009. It is a bold step for South Africa in adopting this multifaceted approach in the implementation of antibiotic stewardship by placing an emphasis on infection prevention and control (Gelband & Duse, 2011:596). Since its inception in 2009, the antibiotic stewardship programme has seen positive impacts in some hospitals in the country. The introduction of the programme in Netcare Sunninghill Hospital saw a reduction in length of stay, admissions and duration of antibiotic therapy with improved patient outcomes (Hewitt, 2013). According to Bala *et al*. (2013:14-18), Dr George Mukhari hospital (Ga-Rankuwa, Gauteng) shared similar experiences with the inception of the programme.

Countries such as the United States (Agwu *et al.,* 2008:751; Fishman, 2006:55; Owens *et al.,* 2004:2008: 896), India (Voss & Ghafur, 2013:2) and most European countries (Allerberger *et al*., 2009:1176; Gould, 1999:257; Nathwani *et al.,* 2012:1-2; Pan *et al.,* 2013:178) have all embraced the concept of the antibiotic stewardship programme.

2.5.4 Measuring the outcomes of interventions

Measuring the outcomes of implemented interventions is expedient to assess their effectiveness. The following parameters are recommended to assess the efficacies of strategies (Brown, 2005:180-181):

- Auditing compliance of the interventions;
- Monitoring changes in total drug usage expressed in terms of the defined daily dose (DDD) before and after implementation;
- Monitoring changes in the usage of targeted drugs in DDD before and after implementation;
- Monitoring changes in mean durations of antibiotic prescription; and
- Monitoring changes in mean duration of hospital stay.

2.6 Quantitative measurement of antibiotic use

Antibiotic resistance, without a doubt, has become a global health concern. There have been several national and international strategies to solve the problem of resistance. These strategies include monitoring resistance patterns and antibiotic use, and a reduction of disease burden through infection control measures and vaccination. In view of the fact that increased antibiotic use is directly linked to the increase in antibiotic resistance, information on the use of antibiotics is of central importance (Finch *et al.,* 2004:44; MacKenzie *et al*., 2005:941). Appropriate methods to measure the use of antibiotics are therefore crucial in order to determine the effectiveness of interventions instituted (Fridkin *et al.,* 1999:245).

Levy (1997:3) proposed the theory that antimicrobial resistance can be minimised if the total antibiotic use in a setting stayed below a critical quantitative level. This theory was based on the assumption that the natural competition among micro-organisms and the potential for the return of their susceptibility after antimicrobial therapy were a possibility that decreased with increased antibiotic use.

In a survey by Lawton *et al*. (2000:258), it was noted that most healthcare institutions were more likely to have programmes optimising the use of antibiotics than participating in population-level surveillance of antibiotic consumption and analysis. Few published data on antibiotic use are available, especially in South Africa, and the lack of reliable data has hindered rational discussions on antibiotic use both in the hospital and community settings (Essack *et al*., 2011:564). Additionally, the major challenge with these published data is the

varying units in which antibiotic use is measured. This makes it quite challenging to compare consumption data with other hospitals or countries.

It has been established that antibiotics are misused by both healthcare professionals and patients (Adorka *et al*., 2013:347; Chukwuani *et al.*, 2002: 18; Guar & English, 2006:343; Mukonzo *et al*., 2013:303; Plachouras *et al.*, 2010:3; Radyowijati & Haak, 2002:8; Sakpota *et al*., 2010:6); however, few studies have been aimed at describing or comparing the use of antibiotics. This has created a barrier in introducing rational discussions about the desirable level of use. Comparing the level of use with other countries can help answer the question, "What is the right or considerable amount of antibiotics to be used by a country?" and whether that level is appropriate (Hutchinson *et al.,* 2004:29).

According to the WHO (2013:25), the quantitative measurement of antibiotic use is essential for the following reasons:

- enactment of policies for the control of antimicrobial resistance;
- comparison of the use of antimicrobials at different levels of healthcare;
- inform and educate stakeholders;
- correlate data from antimicrobial resistance monitoring in humans, animals and food;
- apply risk analysis processes pertaining to the issue of antimicrobial resistance; and
- evaluate the impact of implementation of the prudent use of antimicrobials and of other interventions.

2.6.1 Units to describe drug consumption

Numerous units of measurement have been used to describe antibiotic use with varying data sources. The subsequent paragraphs outline the common units used in quantifying the use of drugs in healthcare institutions.

- **Cost**

The use of drugs can be expressed in terms of cost, for example, in rands. The first drug statistics were done utilising cost figures. Cost studies are useful in analysing expenditure on drugs and evaluating health policies. Additionally, they are beneficial in providing answers to how much a society spends on drugs with respect to the total amount spent per individual, percentage of healthcare cost and percentage of a gross national product (GNP) (Haaijer-Ruskamp & Dukes, 1993:128). However, comparison based on costs is often

misrepresentative due to price differences between different formulations and different national cost levels. Fluctuation in currencies, currency exchange rates, regulatory policies, import duties resulting in changes in the prices of drugs may not permit the long-term assessment of drug use applying cost figures (Haaijer-Ruskamp & Dukes, 1993:130). The increased use of more expensive drugs may have a great influence on the overall cost and *vice versa,* reflecting a false picture on consumption (WHO, 2003:39).

- **Prescription volume**

The number of prescriptions is used to quantify drug use. The total number of prescriptions may not provide a good assessment of total use, unless total amounts of drugs per prescription are also considered (WHO, 2003:39). Quantifying drug use using prescriptions must include the diagnoses, which are often not included on most prescriptions (Capella, 1993:61).

- **Number of units sold**

The use of drugs can also be expressed in terms of the number of units dispensed or sold (Capella, 1993:59). This is applicable when the use of a well-defined product is being evaluated. However, quantifying drug use in this form is unreliable because of variations in packing sizes and strength across countries. The challenge in using physical units of measurement is that drugs with low efficacy may have a larger fraction of the total than drugs with higher efficacy. Furthermore, the use of drugs expressed in the total count of tablets will results in low strength preparations and short-acting preparations contributing more than high strength and longer-acting preparations, respectively (WHO, 2003:39).

There are many studies quantifying drug use, but they have been reported using different methods and measuring units (Adriaenssens *et al*., 2011a:6; Aswapokee *et al*., 1990:138; Harbarth *et al*., 2002:1463; Kritsotakis & Gikas, 2006:703; Kuster *et al*., 2008:553; Polk *et al*., 2007:668).

According to MacKenzie and Gould (2005:105), a meaningful unit must consist of a numerator that represents the amount of antibiotic use, and a denominator that controls the population size. The choice of the numerator is highly relevant to express and compare antibiotic use. A unit of measurement and method of data management independent of sale prices and packages sizes are mostly ideal. The unit must preferably be based on individual prescriptions. The challenge with this method is the unavailability of these prescriptions in

most settings (MacKenzie & Gould, 2005:105). In order to address the concern of a universal system and unit of measurement, it was expedient to have a universal classification system and a unit of measurement to evaluate and compare drug use.

2.6.2 The concept of DDD and ATC classification systems

The daily defined dose (DDD) established by the World Health Organization in 1996 has gained legitimacy and less objectiveness in the measurement of drug use (WHO, 2003:33). This approach has solved the challenge of standardising prescriptions of antibiotics use data. The concept of the DDD is to help monitor and benchmark the use of antibiotics in different countries. Even though the ATC/DDD system for all drugs has been available since the 1980s, it was less understood and used resulting in conflicting publications on antibiotic use (Kuster *et al*., 2008:549).

2.6.2.1 The anatomical therapeutic chemical (ATC) classification system

In the anatomical therapeutic chemical (ATC) classification system, drugs are categorised into 14 main groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties.

The main groups of the ATC classification system are divided into 14 main groups listed in Annexure A. The fourteen major groups are stratified at five different levels. The first level represents the anatomical group and the second level denotes the pharmacological/therapeutic subgroups. The third and fourth levels are the pharmacological/therapeutic and chemical/pharmacological/therapeutic subgroups, respectively. The fifth level is the subgroup for the chemical substance. A complete classification of ciprofloxacin illustrates the structure of the code in Table 2.14 (WHO, 2013:10).

Table 2.14 Classification of ciprofloxacin based on the anatomical therapeutic chemical (ATC) classification system

ATC classification	ATC category	Description
J	General anti-infectives for systemic use	1st level, anatomical group
J01	Antibacterial for systemic use	2nd level, therapeutic main group
J01M	Quinolone antibacterial	3rd level, therapeutic/pharmacological subgroup
J01MA	Fluoroquinolones	4th level, chemical/therapeutic/pharmacological subgroup
J01MA01	Ciprofloxacin	5th level, subgroup for chemical substance

2.6.2.2 Principles for ATC classification

In the anatomical therapeutic classification, drugs are grouped according to the clinical use of the main active ingredient on the basic principle of only one ATC code for each route of administration. Additionally, pharmaceutical forms with similar active ingredients and strength have the same ATC code. The same ATC code is also assigned to drugs of immediate and slow release. A drug can be assigned more than one ATC code if it is available in more than one strength and routes of administration with different clinical uses.

Plain products are defined by the WHO (2013:24) as preparations containing one active compound or medicinal product that, in addition to an active compound, contains auxiliary substances intended to increase the stability of the preparation, and increase the duration or absorption. Plain products are classified according to the general principle explained above.

Combination products are preparations containing two or more active ingredients (WHO, 2013:24). Combination products belonging to the same fourth level are normally classified using the fifth level codes – 20 or 30. Combination products with two or more active ingredients not belonging to the same fourth level are classified using the - 50 series (WHO, 2013:24).

2.6.3 The defined daily dose (DDD)

The definition of the defined daily dose (DDD) is the assumed average maintenance dose per day for a drug used for its main indication in adults. DDDs are only assigned for drugs with ATC codes (WHO, 2003:20). The DDD is a unit of measurement and it is not a reflection of the prescribed daily dose. The DDD is unique for every assigned ATC code and route of administration. The DDD reflects the average adult dose used for the main

indication; even special pharmaceutical forms intended for children are assigned the DDD for adults (WHO, 2013:25). The DDD gives a unit of measurement not influenced by price, currencies, package size and strength.

The DDD per 1 000 inhabitants per day provides a rough estimate of the study population that is treated daily with a particular drug. This estimate is most useful for drugs for chronic diseases. The adjustment of population is considered here most often to correct for differing demographic factors (WHO, 2013:26).

The DDD per 100 bed-days is often used to evaluate drug use when in-patients are being considered. The bed-days must be adjusted for the occupancy rate as the definition of bed-days may vary from institutions. This unit is very useful for benchmarking in hospitals (WHO, 2013:26).

The DDD per inhabitants per year is an estimate of the average number of days for which each inhabitant is treated annually, e.g. 10 DDDs per inhabitant per year implies that the use of a drug is equivalent to the treatment of every inhabitant with a ten-day course during a certain year (WHO, 2013:26).

Prescribed daily dose (PDD) can be defined as the average dose prescribed according to a representative sample of prescriptions (WHO, 2003:20). This can be determined from studies of prescriptions, medical and pharmacy records and patient interviews.

2.7 Chapter summary

In this chapter, antibiotics were defined and a summary of the various sub-pharmacological groups was provided. Cursory analyses of the patterns of antibiotic usage globally were performed. The irrational use of antibiotics was found to be a significant correlation to the emergence of antibiotic resistance. Interventions set up to promote the prudent use of antibiotics were identified, narrowing it to the quantitative measurement of antibiotic use employing the Anatomical Therapeutic Classification (ATC) system and the defined daily dose (DDD) as a unit of measurement developed by the WHO. The next chapter (Chapter 3) will focus on the results and discussions of the empirical investigation phase of the study. The results and discussion are presented in the form of three manuscripts.

CHAPTER 3: RESULTS AND DISCUSSION

3.1 Introduction

This chapter focuses on the results and discussion of the empirical investigation of the study presented in an article format. The results and discussion are presented in three manuscripts parts addressing the main objectives of the empirical investigation.

Manuscript one addressed the objective: investigating the prescribing patterns *viz*. age, gender, seasonal and geographic variations over the eight year period for the various pharmacological groups of antibiotics. Manuscript one was submitted to the Southern African journal of infectious diseases.

Manuscript two addressed the objective: investigating specifically the prescribing patterns of the various groups of fluoroquinolones in adults focusing on longitudinal prevalence variations using the defined daily dose (DDD) per a 1 000 inhabitants per day as a unit of measurement. Manuscript two was submitted to the Journal of antimicrobial chemotherapy.

Manuscript three addressed the objective: describing the prescribing patterns of the various groups of fluoroquinolones in children *viz*. age, gender and speciality of prescribers over the study period; comparing the prescribed daily dosages (PDD) to the recommended daily doses (RDD). Manuscript three was submitted to Biomedical central paediatrics.

Each manuscript conformed to the guidelines for authors per requirement for each journal.

Additional results are presented at the end of this chapter.

3.2 Manuscript one

Article title

Antibiotic prescribing patterns in the South African private health sector (2005-2012)

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ABSTRACT

Background

There is global concern to control antibiotic usage, mainly because of an increase in infections and the use of antibiotics. This study was aimed at investigating longitudinal antibiotic prescribing patterns in the private health sector of South Africa.

Method

A longitudinal retrospective drug utilisation review was conducted using nationally representative claims data from a South African Pharmaceutical Benefit Management company for the period January 2005 to December 2012. Patients were grouped by gender, age and province. Each year was divided into four-month periods to analyse seasonal trends. Prevalence of patients receiving antibiotics, antibiotic prescription prevalence, average number of prescriptions per patient and prevalence of pharmacological groups of antibiotics were determined.

Results

During the study, 44.8% (n = 5 155 262) of patients received at least one antibiotic prescription. The prevalence of patients receiving antibiotic prescriptions decreased by 7.9%. Antibiotic prescriptions were higher in females (n = 2 831 686, 54.9%) and mostly prescribed for patients aged 0 to 18 years (26.5%) and least in patients above 65 years (9.5%). The prevalence of patients receiving antibiotic prescriptions was highest in Gauteng (41.9%) and least in the Northern Cape (1.7%). Antibiotic prescriptions were highest during the winter period. Penicillins were the most prescribed antibiotics (43.1%) and carbapenems the least (0.1%). No practical association was found between antibiotic prescribing and gender, age, province and season.

Conclusion

Antibiotic prescribing has generally decreased in the private health sector of South Africa. Gender, age, province and season were weak predictors of antibiotic prescribing.

Keywords: antibiotics, prescriptions, patterns, gender, age, seasons, provinces

Introduction

Approximately 50% of patients who visit healthcare institutions are prescribed with at least one antibiotic agent. [1, 2] Despite its wide usage, little data exist on the patterns of use in most healthcare settings. [3] This has created a barrier in introducing rational discussions about the desirable level of use. [4] In 2001, The European Centre for Disease Control (ECDC) initialised the European Surveillance on Antibiotic Consumption (ESAC) project. [5] This project was aimed at monitoring antibiotic consumption in all European countries and determining the population's exposure to antibiotics. A similar study has also been done in the United States. [6] South Africa, however, has very little published data on the patterns of antibiotic use. [3] In South Africa, antibiotic consumption in the private sector is derived from Institute of Medical Statistics (IMS) with data collected from wholesalers and direct sales from manufacturers to pharmacies. [3] The data from 2009 and 2010 indicated an increment in the use of antibiotics by approximately 6.5%, with broad spectrum penicillins, carbapenems and macrolides accounting for approximately 43% of the market share. [3] This present study was aimed at investigating the antibiotic prescribing patterns by age and gender, as well as seasonal and geographical distribution over the eight-year period in the private health sector of South Africa.

Method

We conducted a retrospective drug utilisation review analysing nationally representative medicine claims data for an eight-year period (1 January 2005 to 31 December 2012) submitted to a privately-owned South African Pharmaceutical Benefit Management (PBM) company. The data represent a third of South African patients with private medical aid. The target population consisted of 11 502 511 patients of which 5 155 262 (44.8%) patients (study population) claimed antibiotic prescriptions during the study period.

Variables

Variables (age groups, gender, geographical area and seasons) were expressed using descriptive statistics such as frequencies (n), percentages (%), means, standard deviations and 95% confidence intervals (CI). Patients' ages were determined on the date of the next year following the treatment date and divided into four groups: children and adolescents (>0 and ≤18 years); young adults (>18 and ≤30 years); older adults (>30 and ≤45 years and >45 and ≤65 years); and the elderly (>65 years). The nine provinces of South Africa *viz*. Eastern Cape,

Free State, Gauteng, Limpopo, Northern Cape, North West, Mpumalanga, KwaZulu-Natal and Western Cape were used as the main geographical areas. To determine a possible seasonal influence on antibiotic prescribing patterns, each year (1 January to 31 December) was divided into three categories of four-month periods *viz*. January to April, May to August and September to December.

Statistical analyses

Descriptive and inferential statistics were used to analyse the data using the SAS Version 9.3. [7] All statistically significant results were considered with a probability of $p < 0.05$. The practical significance of results was computed when the *p*-value was statistically significant ($p \leq 0.05$).

A two-sample independent *t*-test was used to compare the average number of antibiotic prescriptions per patient per year by gender. A one-way ANOVA, operationalised by the general linear model (GLM) procedure, was used to compare the differences between the average number of antibiotic prescriptions per patient per year between the different age groups and provinces. Tukey's multiple comparison test was performed to determine which groups differ significantly from each other. Cohen's *d* was used to evaluate the effect size between the groups based on the mean values (with $d \geq 0.8$ defined as a large effect with practical significance). A chi-square test (χ^2) was used to determine whether an association exists between the prevalence of antibiotic items per prescription and gender, age groups, seasons or provinces. The chi-square test (χ^2) was also used to determine whether an association exists between the pharmacological groups of antibiotics prescribed in the different years. 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).

Ethics

This study was approved by the Ethics Committee of the North-West University (NWU-0046-08-550) and the board of directors of the South African Pharmaceutical Benefit Management Company (PBM). Data were analysed anonymously. Data privacy and confidentiality were maintained at all times; therefore, no patient or medical scheme/administrator could be traced. Additionally, it was not possible to determine which prescribers or providers (i.e. name of the prescriber/provider) were involved in the

prescribing/dispensing of the medicine items. The PBM providing the data for the study is furthermore nowhere identified in this study. The researcher, study promoter and co-promoter furthermore signed confidentiality agreements.

Results

Antibiotic use and study population

Patients receiving antibiotics decreased from 2005 (46.1%) to 2012 (38.2%); however, peaking in 2007 at 49.0% (Table 1). Of the 64 132 203 prescriptions claimed during the study period, 17.6% (n = 11 309 203) represented the total number of antibiotic prescriptions. Antibiotic agents represented 7.9% (n = 11 986 624) out of the 152 489 789 medicine items claimed. The number of prescriptions and antibiotic agents generally decreased from 2005 to 2012 (Table 1). The average number of antibiotic prescriptions per patient per year ranged from 2.22 ± 1.89 (95% CI 2.22-2.22) in 2005 to 1.98 ± 1.62 (95% CI 1.98-1.99) in 2012. The number of antibiotics per prescription per year remained fairly constant at 1.05 ± 0.19 (95% CI 1.05-1.05) in 2005 to 1.06 ± 0.21 (95% CI 1.06-1.06) in 2012.

Table 1 Distribution of patients claiming antibiotics, antibiotic prescriptions and number of antibiotics claimed during the study period

Year	Total number of patients in database	Number of patients claiming antibiotics, n (%)*	Total number of prescriptions in database	Number of antibiotic prescriptions, n (%) ǂ	Average number of antibiotic prescription per patient ± SD (95% CI)	Total number of medicine items in database	Number of antibiotic claimed, n (%)Ψ	Average number of antibiotic per prescription ± SD (95% CI)
2005	1 712 172	789 247 (46.1)	8 436 901	1 752 779 (20.8)	2.22 ± 1.89 (2.22 - 2.22)	19 500 774	1 857 824 (9.5)	1.05 ± 0.19 (1.05 - 1.05)
2006	1 757 926	803 415 (45.7)	8 951 720	1 849 677 (20.7)	2.30 ± 1.97 (2.30 - 2.31)	21 113 403	1 958 577 (9.3)	1.05 ± 0.19 (1.05 - 1.05)
2007	1 355 268	664 474 (49.0)	7 956 538	1 547 028 (19.4)	2.33 ± 1.95 (2.32 - 2.33)	19 075 705	1 638 741 (8.6)	1.05 ± 0.19 (1.05 - 1.05)
2008	1 123 660	533 334 (47.5)	6 819 678	1 214 111 (17.8)	2.28 ± 1.91 (2.27 - 2.28)	16 439 253	1 289 027 (7.8)	1.05 ± 0.20 (1.06 - 1.06)
2009	1 537 385	709 308 (46.1)	9 091 934	1 547 721 (17.0)	2.18 ± 1.75 (2.18 - 2.19)	21 648 991	1 639 988 (7.6)	1.05 ± 0.20 (1.05 - 1.06)
2010	1 455 737	637 133 (43.8)	8 588 146	1 358 941 (15.8)	2.13 ± 1.74 (2.13 - 2.14)	20 527 777	1 436 642 (7.0)	1.05 ± 0.19 (1.05 - 1.05)
2011	1 302 431	538 192 (41.3)	7 441 285	1 087 053 (14.6)	2.02 ± 1.63 (2.02 - 2.20)	17 766 594	1 151 168 (6.5)	1.05 ± 0.20 (1.05 - 1.05)
2012	1 257 932	480 159 (38.2)	6 846 001	951 920 (13.9)	1.98 ± 1.62 (1.98 - 1.99)	16 409 292	1 014 657 (6.2)	1.06 ± 0.21 (1.06 - 1.06)
TOTAL	**11 502 511**	**5 155 262 (44.8)**	**64 132 203**	**11 309 230 (17.6)**		**152 489 789**	**11 986 624 (7.9)**	

* ǂ ΨPercentages were calculated according to the total in each respective year

The ratio of females to males was 1.2:1. The frequency of antibiotic prescriptions was higher in females (n = 2 831 686, 54.9%) than in males (n = 2 321 635, 45.0%) over the study period; however, there was no practical association between the average number of antibiotic prescriptions and gender ($p < 0.0001$, Cohen's d-value < 0.2). The highest prevalence of patients receiving antibiotic prescriptions was observed in patients between 0 and 18 years, though decreasing from 29.4% (n = 232 132) in 2005 to 24.7% (n = 118 808) in 2012, followed by patients between 45 and 65 years, increasing from 23.4% (n = 184 312) to 26.5% (n = 127 002). The lowest prevalence of antibiotic prescriptions was observed in ages above 65 years. There was, however, no practical association between average number of antibiotic prescriptions in the different age groups ($p < 0.0001$, Cohen's d-value < 0.2) (Table 2).

Table 2 Antibiotic prescription per patient stratified by gender, age and province

Subgroup	Number of patients claiming antibiotics, n (%)[§] 2005 (N = 789 247)	2006 (N = 803 415)	2007 (N = 664 474)	2008 (N = 533 334)	2009 (N = 709 308)	2010 (N = 637 133)	2011 (N = 538 192)	2012 (N = 480 159)	Relative change 2005 *vs.* 2012 (%)	*p*-value
Gender										
Female	438 243 (55.5)	446 340 (55.6)	370 512 (55.8)	297 191 (55.7)	388 768 (54.8)	347 459 (54.5)	290 223 (53.9)	252 950 (52.7)	-2.8	< 0.0001
Male	349 888 (44.3)	356 439 (44.4)	293 779 (44.2)	236 143 (44.3)	320 540 (45.2)	289 674 (45.5)	247 966 (46.1)	227 206 (47.3)	+3.0	
Unidentified gender	1 116 (0.2)	636 (0.08)	183 (0.03)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.0006)	3 (0.0006)		
Age groups (years)										
>0, ≤18	232 132 (29.4)	230 546 (28.7)	183 242 (27.6)	129 253 (24.2)	183 307 (25.8)	158 446 (24.9)	132 537 (24.6)	118 808 (24.7)	-4.7	< 0.0001
>18, ≤30	106 193 (13.5)	112 523 (14.0)	94 051 (14.2)	72 799 (13.7)	111 217 (15.7)	99 629 (15.6)	82 286 (15.3)	71 895 (15.0)	+1.5	
>30, ≤45	202 058 (25.6)	201 322 (25.1)	159 319 (24.0)	123 152 (23.1)	160 876 (22.7)	144 230 (22.6)	123 967 (23.0)	111 855 (23.3)	-2.3	
>45, ≤65	184 312 (23.4)	193 784 (24.1)	170 033 (25.6)	153 763 (28.8)	184 269 (26.0)	166 968 (26.2)	140 439 (26.1)	127 002 (26.5)	+3.1	
> 65	64 552 (8.1)	65 240 (8.2)	59 362 (8.9)	54 367 (10.2)	69 553 (9.8)	67 860 (10.7)	58 963 (11.0)	50 599 (10.5)	-2.4	
Province										
Gauteng	309 711 (39.2)	328 990 (41.0)	272 378 (41.0)	220 795 (41.4)	309 555 (43.6)	279 384 (43.9)	234 349 (43.5)	204 198 (42.5)	+3.3	< 0.0001
KwaZulu-Natal	118 928 (15.0)	117 375 (14.6)	101 585 (15.3)	83 882 (15.7)	102 279 (14.4)	85 411 (13.4)	69 378 (12.9)	59 179 (12.3)	-2.7	
Western Cape	74 869 (9.5)	73 520 (9.2)	63 014 (9.5)	50 203 (9.4)	73 180 (10.3)	65 134 (10.2)	52 959 (9.8)	48 143 (10.0)	+0.5	
Limpopo	61 964 (7.9)	63 431 (7.9)	50 653 (7.6)	37 620 (7.1)	36 233 (5.1)	30 011 (4.7)	25 359 (4.7)	22 800 (4.8)	-3.1	
Eastern Cape	57 572 (7.3)	52 413 (6.5)	41 466 (6.2)	34 699 (6.5)	44 833 (6.3)	39 941 (6.3)	32 850 (6.1)	30 157 (6.3)	-1.0	
North West	50 601 (6.4)	56 922 (7.19)	48 193 (7.3)	36 507 (6.9)	48 322 (6.8)	45 215 (7.1)	37 400 (7.0)	35 003 (7.3)	+0.9	
Mpumalanga	47 726 (6.1)	55 436 (6.9)	45 840 (6.9)	36 363 (6.8)	48 851 (6.9)	46 561 (7.3)	44 263 (8.2)	42 124 (8.8)	+2.7	
Free State	33 983 (4.3)	35 527 (4.4)	27 896 (4.2)	23 337 (4.4)	31 710 (4.5)	30 589 (4.8)	26 834 (5.0)	24 240 (5.1)	+0.8	
Northern Cape	13 554 (1.7)	13 115 (1.6)	10 489 (1.6)	8 070 (1.5)	10 265 (1.5)	10 765 (1.7)	10 747 (2.0)	10 715 (2.2)	+0.5	
Unidentified	20 339 (2.6)	6 686 (0.8)	2 960 (0.5)	1 858 (0.4)	4 080 (0.6)	4 122 (0.7)	4 053 (0.8)	3 600 (0.8)	-1.8	

[§] Percentages were calculated according to the total number of patients claiming antibiotics in each respective year.

Gauteng had the highest prevalence of patients receiving antibiotics, increasing from 39.2% (n = 309 711) in 2005 to 42.5% (n = 204 198) in 2012. The Northern Cape had the lowest prevalence of patients claiming antibiotics, however, increasing from 1.7% (n = 13 554) in 2005 to 2.2% (n = 10 715) in 2012 (Table 2). Patients receiving antibiotics in Limpopo, KwaZulu-Natal and the Eastern Cape decreased by 3.1%, 2.7% and 1.0% respectively during the study period (Table 2). There was no practical association between the prevalence of patients receiving antibiotics in the different provinces ($p < 0.0001$, Cramer's $V \leq 0.2$).

The prescribing of antibiotics was highest from May to August, representing the winter season in South Africa. Conversely, the prescribing of antibiotics was least January to April. There was, however, no practical association throughout the study period between antibiotic prescribing and seasonal trends ($p < 0.0001$, Cramer's < 0.2).

Antibiotics prescribing

The penicillins were the most frequently prescribed antibiotics with relative use decreasing from 44.5% (n = 825 997) in 2005 to 43.2% (n = 438 537) in 2012. This was followed by the fluoroquinolones, with no significant change in the level of prescribing, remaining constant from 16.3% in 2005 and 16.2% in 2012. The use of macrolides increased from 12.8% in 2005 to 15% in 2012. The carbapenems and chloramphenicols were the least prescribed in all age groups. The use of carbapenems increased from 0.001% in 2005 to 0.02% in 2012 (Table 3). Though statistically significant, there was no practical association between the number of antibiotic agents claimed and age, gender or season ($p < 0.0001$, Cramer's $V < 0.2$).

Table 3 Pharmacological groups of antibiotics prescribed during the study period

	Medicine items claimed, n (%)**									
Pharmacological group	**2005 (N = 1 857 824)**	**2006 (N = 1 958 577)**	**2007 (N = 1 638 741)**	**2008 (N = 1 289 027)**	**2009 (N = 1 639 988)**	**2010 (N = 1 436 642)**	**2011 (N = 1 151 168)**	**2012 (N = 1 014 657)**	**Relative change '05 *vs.* '12 (%)**	***p*-value**
Penicillins	825 997 (44.5)	870 036 (44.4)	699 379 (42.7)	552 512 (42.9)	694 653 (42.4)	593 645 (41.3)	491 370 (43.2)	438 537 (43.2)	-1.3	
Quinolones	303 318(16.3)	326 384 (16.7)	291 361 (17.8)	232 849 (18.1)	288 161 (17.6)	255 982 (17.8)	193 742 (16.8)	164 617 (16.2)	-0.1	
Cephalosporins	285 531 (15.4)	283 576 (14.5)	235 902 (14.4)	166 709 (12.9)	227 393 (13.9)	196 139 (13.7)	149 889 (13.0)	133 344 (13.1)	-2.3	
Macrolides	237 303 (12.8)	264 922 (13.5)	234 060 (14.3)	183 307 (12.2)	247 938 (15.1)	220 220 (15.3)	176 465 (15.2)	152 035 (15.0)	+2.2	
Sulphonamides/ Trimethoprim	99 074 (5.3)	110 909 (5.7)	93 980 (5.7)	86 867 (6.7)	101 682 (6.2)	100 061 (7.0)	85 757 (7.5)	78 889 (7.8)	+2.5	< 0.0001
Tetracyclines	97 172 (5.3)	93 355 (4.8)	74 784 (4.6)	59 278 (4.6)	67 694 (4.1)	58 239 (4.1)	45 396 (3.9)	40 286 (4.0)	-1.3	
Aminoglycosides	7 760 (0.4)	8 199 (0.4)	8 266 (0.5)	6 702 (0.5)	8 996 (0.6)	7 239 (0.5)	5 797 (0.5)	6 170 (0.6)	+0.2	
Chloramphenicol	1 652 (0.09)	1 177 (0.06)	982(0.06)	773 (0.06)	824 (0.05)	1 009 (0.07)	849 (0.07)	554 (0.05)	-0.04	
Carbapenems	17 (0.001)	19 (0.001)	27 (0.002)	30 (0.002)	2 646 (0.2)	4 108 (0.3)	1 903 (0.2)	225 (0.02)	+0.02	

**Percentage was calculated according to the total medicine items claimed for each year

The broad-spectrum penicillin (amoxicillin-clavulanic acid) was the most prescribed antibiotic during the study period ranging from 25.7% in 2005 to 27.3% in 2012. Among the macrolides, azithromycin and clarithromycin were observed to have a relative increase of 2.6% and 1% respectively from 2005 to 2012. The prescribing of sulphadoxine/trimethoprim increased from 5.3% in 2005 to 7.8% in 2012. A notable decrease in prescribing was observed in amoxicillin, cefaclor and erythromycin, with a cut-off point set at ±0.7% (Table 4). The prescribing of these three antibiotics decreased by 2.2, 1.4 and 0.9%, respectively.

Table 4 Notable relative changes in specific antibiotic agents from 2005 to 2012 (%)

Antibiotic agent	2005	2006	2007	2008	2009	2010	2011	2012	Relative change 2005 vs. 2012
					Increase				
Amoxicillin/clavulanic acid	477 168 (25.7)	52 2050 (25.7)	432 832 (26.4)	353 407 (27.4)	450 654 (27.5)	37 7641 (26.3)	31 0051 (26.9)	273 433 (27.0)	1.3
Ciprofloxacin	157 264 (8.5)	170 663 (8.7)	150 828 (9.2)	120 524 (9.4)	148 966 (9.1)	137 261 (10.0)	105 945 (9.2)	93 574 (9.2)	0.7
Sulphadoxine/Trimethoprim	9 9074 (5.3)	110 909 (5.7)	93 980 (5.7)	86 867(6.7)	101 659 (6.2)	100 061(7.0)	85 757 (7.5)	78 889 (7.8)	2.5
Clarithromycin	94 400 (5.1)	109 462 (5.6)	99 528 (6.1)	73 439 (5.7)	101 434 (6.2)	92 010 (6.4)	72 848 (6.3)	61 809 (6.1)	1.0
Cefpodoxime	75 412 (4.1)	80 871 (4.1)	72 552 (4.4)	48 194 (3.7)	80 021 (4.9)	73 651 (5.1)	57 495 (5.0)	47 443 (4.7)	0.6
Azithromycin	46 880 (2.5)	57 549 (2.9)	57 991 (3.5)	51 613 (4.0)	81 604 (5.0)	72 560 (5.1)	59 553 (5.2)	52 018 (5.1)	2.6
Moxifloxacin	42 819 (2.3)	51 651 (2.6)	52 156 (3.2)	39 084 (3.0)	47 648 (2.9)	41 945 (2.9)	33 660 (2.9)	27 864 (2.8)	0.5
Levofloxacin	41 354 (2.2)	51 095 (2.6)	51 401 (3.1)	47 637 (3.7)	66 860 (4.1)	57 956 (4.0)	41 684 (3.6)	33 552 (3.3)	1.1
Ceftriaxone	14 820 (0.8)	16 657 (0.9)	14 985 (0.9)	13 223 (1.0)	17 810 (1.1)	15 944 (1.1)	13 427 (1.2)	15 875 (1.6)	0.8
					Decrease				
Amoxicillin	279 120 (15.0)	275 247 (14.1)	205 019 (12.5)	152 840 (11.9)	185 189 (11.3)	1 70315 (11.9)	144 699 (12.6)	129 926 (12.8)	-2.2
Doxycycline	65 309 (3.5)	62 270 (3.2)	49 058 (3.0)	39 159 (3.0)	44 453 (2.7)	39 781 (2.8)	32 109 (2.8)	28 378(2.8)	-0.7
Erythromycin	62 426 (3.4)	58 899 (3.0)	47 871 (2.9)	35 795 (2.8)	39 299 (2.4)	33 649 (2.3)	28 589 (2.5)	25 082 (2.5)	-0.9
Cefaclor	32 399 (1.7)	25 859 (1.3)	11 817 (0.7)	6 171 (0.5)	6 768 (0.4)	5 260 (0.4)	3 936 (0.3)	3 090 (0.3)	-1.4
Ofloxacin	15 857 (0.9)	16 336 (0.8)	11 929 (0.7)	7 904 (0.6)	5 954 (0.4)	3 997 (0.3)	1 898 (0.2)	1 932 (0.2)	-0.7

Discussion

This large longitudinal study showed that total antibiotic use by patients decreased by approximately 7.9% from 2005 to 2012. The penicillins and fluoroquinolones were the most prescribed pharmacological group of antibiotics in this section of the private health sector of South Africa. This trend confirms other studies conducted in Europe [5] and in South America. [8] For example, Adriaenssens *et al*. [5] observed penicillins being widely prescribed in 33 European countries, followed by the fluoroquinolones and macrolides from 1997 to 2009. However, in the United States [6], tetracycline, macrolides and fluoroquinolones were the most widely prescribed antibiotics. It was interesting to note the gradual increase in the use of broader spectrum antibiotics and a decline in the use of older antibiotics, confirming this trend from studies done in European countries. The shift to these antibiotics has been attributed to increased resistance to older antibiotics; major advancement in the diagnoses of diseases; availability of these agents; better compliance as these antibiotics have flexible dosage regiments; and fewer side effects associated with these antibiotics. [5, 9] The decrease in total antibiotic use may be attributed to awareness and educational programmes aimed at prescribers and patients on the dangers of irrational use; e.g., in 2009, the antibiotic stewardship programme was introduced in the private health sector to promote prudent use. [10]

Though there was no practical association between gender and prescribing prevalence, we observed the prevalence of antibiotics prescribing higher in females than in males. This trend confirms studies done in New Zealand [11] and in the Netherlands. [12] Our observation may be due to the higher population of females than males in the database. These trends reflect the demographic profile of beneficiaries covered by medical aid schemes registered in South Africa in terms of the Medical Schemes annual report. [13] Additionally, according to the national census in South Africa, there are more females than males in the total South African population. [14] According to Verbrugge, health-seeking behaviour varies greatly by gender. [15] Women are more sensitive to discomfort, more likely to perceive symptoms of an illness and are more likely to report health-related issues than men. He attributed his findings to societal expectations where males are encouraged to ignore symptoms of illness to prove their virility. [15]

The study observed the highest antibiotic use in patients between the ages of 0 and 18 years and patients between 45 and 65 years. Population statistics in South Africa reveal that one-

third of the population are below the age of fifteen years and approximately 7% above the age of 65 years and may account for this observation. [14] These two population subgroups represent children who are still developing immunity and adults with active lifestyles, respectively. Studies have shown that children below 18 years are prone to respiratory tract infections, and therefore they are more likely to be prescribed with an antibiotic. [16]

The provinces of Gauteng and KwaZulu-Natal had the highest number of patients claiming antibiotics during the study period. These are two highly populated provinces in South Africa with approximately 20% of the population residing in these provinces, respectively. [14] Population density, urbanisation and migration may be possible causes of the increased use in antibiotics associated with the increase in infectious diseases. The close proximity in living areas may facilitate the spread of infections and consequently increase the use of antibiotics. [17]

Studies performed in Europe [5] and America [9] have shown that antibiotics are mostly used during the winter period, especially for the treatment of respiratory tract infections. Our study confirms this trend with the highest prevalence in the winter season (May to August). Although the indication for use was not analysed in the study, the magnitude of use of the broad-spectrum penicillins (amoxicillin/clavulanic acid), azithromycin and sulphadoxine/trimethoprim suggests a high incidence of respiratory tract infections during the winter months. [5, 9]

Conclusion

From our study, gender, age, season and geographical areas were weak predictors of antibiotic use. The increase in the use of sulphadoxine/trimethoprim, amoxicillin-clavulanic acid and azithromycin can be attributed to its use in the treatment of respiratory tract infections. We therefore recommend that effective interventions be instituted nationwide to curb antibiotic use particularly during the winter seasons as many of these infections may be of viral origin. Additionally, effective infection control methods should be directed at Gauteng to reduce antibiotic use. We also recommend that future studies be conducted to determine the future implications on the use of new broader-spectrum antibiotics such as amoxicillin/clavulanic acid, azithromycin and levofloxacin; and their evidence in proper infection control.

A limitation of this study was the inability to correlate use with diagnoses due to incomplete data. Some prescribers failed to indicate the diagnoses on the prescriptions issued. It is also not certain whether the antibiotics dispensed were actually consumed by the patient and consequently may not accurately reflect antibiotic use in the population. Finally, the data used represent only a section of patients registered as beneficiaries of medical schemes in South Africa.

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3.3 Manuscript two

Fluoroquinolone utilisation patterns in adults in the private health sector of South Africa (2005-2012)

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SYNOPSIS

Objectives

Fluoroquinolones represent major clinical advancements with their antipseudomonal activity and relatively good clinical profiles. However, little data exist on their pattern of use in South Africa. This study aims to describe their pattern of use in adults in the private health sector of South Africa over an eight-year period (2005-2012).

Method

Prescription data on outpatient fluoroquinolone (J01MA) use at the active ingredient level in patients above 18 years were collected from a nationally representative prescription claims database from 2005 to 2012 using the Anatomical Therapeutic Chemical (ATC)/defined daily dose (DDD) methodology. Fluoroquinolone prescribing was analysed based on age and gender. Overall, fluoroquinolone use patterns were classified into three fluoroquinolone generations and expressed in DDDs/1000 inhabitants/day (DID).

Results

Between 2005 and 2012, a total of 1 983 622 prescriptions for fluoroquinolones were claimed. The highest prevalence of fluoroquinolone prescription was found in females ($p < 0.0001$, Cramer's $V = 0.02$) and in patients between 45 and 65 years ($p < 0.0001$, Cramer's $V = 0.04$). Total fluoroquinolone use decreased from 2.85 DID in 2005 to 2.41 DID in 2012. Norfloxacin was the only first-generation fluoroquinolone prescribed. The second-generation fluoroquinolones accounted for more than 50% of the total DID, with ciprofloxacin being the most used in this generation. Moxifloxacin was the most prescribed third-generation fluoroquinolone; its use ranging from 0.51 DID in 2005 to 0.44 DID in 2012.

Conclusion

Overall, fluoroquinolone use decreased from 2005 to 2012. The use of a medicine claims database, utilising the ATC/DDD methodology, is an effective method of describing and comparing antibiotic use.

Introduction

"*Antimicrobial resistance: no action today – no cure for tomorrow*" [1] – this was the theme for the 2011 World Health Day where antimicrobial resistance was named as one of the three largest health threats to mankind. [2] Over the past seven decades, we have been living in an optimistic world where antibiotics have been seen as 'magic bullets' in the treatment of infectious diseases. [3] Although the issue of antibiotic resistance is not something new, its imprints tend to flaw the major advancements in modern medicine. With the discovery of fluoroquinolones, a major stride in antimicrobial chemotherapy was achieved owing to its antipseudomonal property.[4] This has made them the drug of choice for both complicated respiratory and urinary tract infections in most patient groups.[5, 6]

Fluoroquinolones have become one of the fastest-growing antibiotic groups with regard to use.[7] Approximately 80% of European countries have shown an increase in fluoroquinolone use over the past decade.[7-10] For example, in Greece and Luxembourg, quinolone use increased from 1.11 DID and 1.63 DID in 1997 to 2.63 DID and 2.83 DID' in 2009, respectively.[7] In India, fluoroquinolones are the most used antibiotic group at all healthcare settings.[11, 12] Furthermore, in the United States, fluoroquinolones are the most prescribed antibiotic group in the adult population. Its use in the United States increased threefold from 7 million visits in 1995 to 22 million visits in 2002 due to changes in prescribing patterns for respiratory tract infections and inappropriate prescribing.[13] Latin American countries have also reported an increase in fluoroquinolone use, where, in Venezuela, the use of fluoroquinolones tripled within a ten-year period (+282%).[14]

Although fluoroquinolones are prescribed in South Africa, limited information is available on their pattern of use. Where usage has been correlated with resistance, [15-18] it has become

expedient to monitor antimicrobial usage at all healthcare levels. The objective of this study was to describe the trends in outpatient systemic fluoroquinolone use in patients older than 18 years over an eight-year period in a part of the private health sector of South Africa.

Method

We conducted a retrospective drug utilisation review analysing nationally representative outpatient prescription claims data obtained from a privately-owned South African Pharmaceutical Benefit Management (PBM) company. This database represents a third of the South African private health sector population covered by medical aid. Data for an eight-year period (1 January 2005 to 31 December 2012) for a total of 3 788 438 patients older than 18 years (male/female ratio 1.2:1) claiming at least one antibiotic prescription were obtained from the database. The study population was grouped based on the following variables to determine the prevalence of patients receiving fluoroquinolone prescriptions:

- Gender: Although less than 1% of the study population had no identified gender, they were included to show total fluoroquinolone use.
- Age: Patients' ages were determined on the date of the next year following the treatment date and divided into four groups, namely: young adults (>18 and ≤30 years); older adults (>30 and ≤45 years and >45 and ≤65 years); and the elderly (>65 years).

Fluoroquinolones were defined as all active substances available in South Africa at the time of the study, belonging to the J01MA classification of the ATC index. Data obtained included the NAPPI (National Pharmaceutical Product Index) code (a unique product identifier), the number of dosages dispensed and the number of days' supply. The data obtained were expressed in DDD/1000 inhabitants/day. This was done by determining the total amount of the drug dispensed (in grams), divided by the defined daily doses (DDD) (WHO, version 2013) [19]

conversion factor and the population (using the total number of beneficiaries covered by the medical aid schemes registered under the PBM company during the study period, as denominator for each respective year) to obtain the results in DDD-inhabitants/year. The DDD/inhabitants/year was then divided by 365 days and multiplied by 1 000, to obtain the DDD/1000 inhabitants/day. [20] The average DDD per prescription per patient per year was also determined to describe the trends over the study period. To enable comparison of fluoroquinolone use, active substances were divided into the three generations, as proposed by Ball, [21] who took into account their expanded antimicrobial spectrum and clinical indications.

Data were analysed using SAS version 9.3 software. [22] Statistically significant results were considered with a probability of $p < 0.05$. The practical significance of results was computed when the *p*-value was statistically significant ($p \leq 0.05$). A two-sample independent *t*-test was used to compare the average number of fluoroquinolone prescriptions per patient per year by gender. A one-way ANOVA, operationalised with the general linear model (GLM) procedure, was used to test differences between the average number of fluoroquinolone prescriptions per patient per year, between the different age groups. Tukey's multiple comparison test was performed to determine which groups differ statistically significantly from each other. Cohen's *d*-value was used to test the practical significance of the difference in means between two groups (with $d \geq 0.8$ defined as a large effect with practical significance). A chi-square test (χ^2) was used to determine the association between the prevalence of fluoroquinolone prescriptions and gender and different age groups stratified by the study period. Cramer's *V* statistic was used to test the practical significance of these associations (with Cramer's $V \geq 0.5$ defined as practically significant).

This study was approved by the Ethics Committee of the North-West University (ethics application number NWU-0046-08-550) and the board of directors of the South African Pharmaceutical Benefit Management Company (PBM).

Results

Fluoroquinolone use by study population

During the study period, 36.9% (n = 1 397 960) of the total number of patients who claimed antibiotic prescriptions represented patients who claimed at least one fluoroquinolone prescription. A total of 1 983 622 fluoroquinolone prescriptions and 1 998 552 fluoroquinolone agents were claimed during the study period. The average number of fluoroquinolone prescriptions per patient per year ranged from 1.45 ± 0.92 (95% CI 1.44 - 1.45) in 2005 to 1.31 ± 0.71 (95% CI 1.31 - 1.32) in 2012.

The prevalence of males who received fluoroquinolone prescriptions as a percentage of the total number of patients who received fluoroquinolone prescriptions increased from 38.2% (n = 77 009) in 2005 to 42.3% (n = 51 330) in 2012 compared to a decreasing trend in females (Table 1). The highest prevalence of fluoroquinolone prescriptions was observed in the age group 45 to 65 years, increasing from 34.8% (n = 69 991) in 2005 to 37.1% (n = 45 087) in 2012. No practically significant association was found between the prevalence of fluoroquinolone prescriptions and gender ($p < 0.0001$, Cramer's $V = 0.02$) or age group ($p < 0.0001$, Cramer's $V = 0.04$) during the study period.

See table 1

Average DDD per prescription per patient

Table 2 provides the average DDD per prescription per patient per year for the various fluoroquinolones prescribed during the study period. Though statistically significant differences were found for most fluoroquinolones prescribed, it was not practically significant (Cohen's *d*-value ≤ 0.42).

See table 2

Fluoroquinolone use by generation

Figure 1 shows the compositional trends in fluoroquinolone use by the three generations from 2005 to 2012, expressed in DDD/1000 inhabitants/day (DID). The results show an increasing trend in total fluoroquinolone use from 2.84 DID in 2005 to 3.69 DID in 2007, followed by a decreasing trend from 3.57 DID in 2008 to 2.41 DID in 2012. The second generation fluoroquinolones were the most used throughout the study period, followed by the third generation fluoroquinolones.

Table 3 provides the relative use of fluoroquinolones according to the three generations at the chemical substance level from 2005 to 2012. Norfloxacin was the only first-generation fluoroquinolone; its utilisation decreased from 0.17 DID in 2005 to 0.07 DID in 2012. The most used second-generation fluoroquinolone was ciprofloxacin. Its use ranged from 1.30 DID in 2005 to 1.19 DID in 2012. This was followed by levofloxacin, which increased from 0.46 DID in 2005 to 0.67 DID in 2012; however, peaking at 1.04 DID in 2009. Enoxacin was the least prescribed second-generation fluoroquinolone. It was prescribed from 2005 (0.0005 DID) to 2007 (0.0003 DID). Moxifloxacin accounted for the most used third-generation fluoroquinolone during the study period. Its use decreased from 0.51 DID in 2005 to 0.44 DID

in 2012. The use of gatifloxacin decreased over the study period from 0.19 DID in 2005 to 0.001 DID in 2008, making moxifloxacin the only third-generation fluoroquinolone being prescribed from 2009 to 2012 at a prevalence percentage of 100%.

See Fig. 1

See Table 3

Discussion

This study shows the annual trend in fluoroquinolone use in a part of the private health sector of South Africa. Contrary to other studies, our findings showed overall fluoroquinolone use decreasing over the study period. In a study by Adriaenssens *et al*., [7] most European countries showed an increasing trend in the use of fluoroquinolones from 1997 to 2009, where the highest use was observed in Italy. Wirtz *et al*. [14] also reported an increasing trend in fluoroquinolone use from 1997 to 2007 in eight Latin American countries, with the highest use in Venezuela. In the United States, Linder *et al*. [13] reported a 200% increase in fluoroquinolone prescribing from 1995 to 2002. However, in a recent report by Public Health England, [23] total quinolone use from the community and hospitals decreased from 0.61 DID in 2011 to 0.58 DID in 2013. This decreasing trend was attributed to a decline in *Clostridium difficile* and methicillin-resistant *Staphylococcus aureus* (MRSA) infections.[23]

The first-generation fluoroquinolones, e.g. norfloxacin, are often used to treat urinary tract infections, whereas the second and third generations are mostly indicated for both respiratory and urinary tract infections. [21] Similar to trends in several European countries, we observed a decreasing trend in the use of the first-generation fluoroquinolone (predominantly norfloxacin) over the study period.[7, 8] In their study, Adriaenssens and colleagues[7] attributed this trend in

European countries to emerging resistance. Due to a lack of clinical/diagnostic data, these prescribing trends in our study population could not be verified.

The second-generation fluoroquinolones accounted for at least 75% of the total DID in each year. This trend confirms findings from studies done in Tanzania, [24] Europe, [7, 8] the United States [13, 25] and South America. [14] Ciprofloxacin alone accounted for more than 50% of the total DID in this generation; however, its relative use began to decrease from 2008. Since the 1990s, ciprofloxacin had been used for the syndromic management of gonococci infections until 2003, when there was a rapid emergence of ciprofloxacin-resistant gonococci strains in South Africa. [26] To address the problem, the national guidelines for the treatment of gonococci infections were revised in 2008; making cefixime (oral or intramuscular) the drug of choice. [27, 28] With more than 50% of gonococci cases managed by the private sector, [27] this change in guidelines may explain the decreasing trend in ciprofloxacin prescribing practices from 2008. It is, however, considered the first-line drug for typhoid fever and *Shigella* infections, [21] which are also considered health risks in South Africa. [28]

The average number of DDDs per prescription per patient for levofloxacin was observed to increase across the study period. Levofloxacin is recommended in South Africa for use in the treatment of lower respiratory tract infections, e.g. community acquired pneumonia, in adults.[29, 30] Since the number of DDDs is directly influenced by the quantity supplied, [20] the observed possibly indicates a longer duration of therapy. A study by Schein *et al.* [31] showed that the use of levofloxacin in the treatment of community acquired pneumonia compared to moxifloxacin was more advantageous. Treatment with levofloxacin was associated with shorter hospital days and lower costs, although others report the contrary with regard to better

safety and speed of clinical recovery with moxifloxacin. [32, 33] Pharmaceutical companies enhance the advertising of their drugs before patent expiry to optimise earnings as the generic brands invade the market. [34] The observed increase in use of levofloxacin in 2009 may be due to its patent expiry at the end of 2010. [35]

Similar to other studies, [7, 8, 13] our study showed that moxifloxacin accounted for the most used third-generation fluoroquinolone during the study period. Its use in the South African private health sector is indicated for complicated respiratory tract infections; [29, 30] however, this finding cannot be linked to the prevalence of respiratory tract infections due to a lack of complete data regarding diagnoses.

The use of gatifloxacin was observed from 2005 to 2008 in our study. Complaints surrounding its safety and effectiveness, causing hyperglycaemia in both diabetic and non-diabetic patients,[36] led to the withdrawal of gatifloxacin in 2008 by the Food and Drugs Administration (FDA) of the United States of America. [37] This may serve as a proxy for prescribers' compliance to the FDA guidelines.

The prevalence of fluoroquinolone prescriptions was higher in females. Fluoroquinolones are first-line agents for urinary tract infections in the non-pregnant population in South Africa.[6] Females are furthermore found to be more susceptible to urinary tract infections than men are. Studies have attributed the high incidence of urinary tract infections in women to frequent sexual intercourse and genetic disposition.[38-41] Additionally, antibiotic prescription claim rates have been found to be higher in females.[42, 43] Verbrugge [44] noted in his study that health-seeking behaviour varied greatly by gender. According to Verbrugge, [44] women are more

sensitive to discomfort, more likely to perceive symptoms of an illness and are more eager to report health-related issues than men.[44] Men, on the other hand, are expected by society to ignore symptoms of diseases to prove their masculinity.[44]

Several studies on the use of fluoroquinolones indicate a higher prevalence of fluoroquinolone prescribing in patients 65 years of age, and they indicate that they are mainly used for the treatment of urinary and lower respiratory tract infections common in this group of patients.[10, 45-50] Our study, however, showed that prescribing peaked at an earlier age in patients between 45 and 65 years. These prescribing trends could, however, not be verified in the absence of the patient's diagnosis.

Conclusion

From the study, fluoroquinolone use has generally decreased in the private health sector of South Africa. The relative increase in the use of levofloxacin may be an indication of the prevalence of complicated respiratory tract infections.[29, 30] Interventions to reduce ciprofloxacin-resistant gonococci from 2008 [26, 27] appear to be effective with reference to the decreased ciprofloxacin prescribing patterns over the study period.

Measuring and displaying information on the use of drugs to prescribers, patients and policy-makers are deemed as the first step in creating awareness for rational drug use. [51] The ATC classification and the DDD unit of measurement have also created a platform to compare use levels at different settings and different geographic locations. [20] We recommend that further studies be conducted in other parts of the private or public health sector of South Africa to compare use and help define desirable levels of use.

A limitation to this study was the inability to correlate fluoroquinolone use with diagnoses on the database, as data fields on diagnoses were incomplete. We are also not certain whether fluoroquinolones dispensed were actually consumed by patients and consequently may not reflect actual total fluoroquinolone use in the population. Finally, the data used represent only a section of patients registered as beneficiaries of medical schemes in South Africa.

However, to the best of our knowledge, this is the first study to be conducted measuring fluoroquinolone use according to the ATC/DDD classification system utilising medicine claims data in South Africa. The South African private health sector has coverage of approximately 20% of the country's population, especially for those in employment. Medical aid schemes remain the main means of financing in the South African private health sector. The PBM Company processes approximately 300 000 real-time and 30 000 doctor transactions daily. The reliability and validity of the data are ensured by gate-keeping services, eligibility services, utilisation management services, clinical management services and pricing management along with real-time benefit management.

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Transparency declaration

None to declare.

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Table 1 Distribution of patients claiming antibiotics and fluoroquinolone prescriptions (2005 – 2012)

Study period	2005	2006	2007	2008	2009	2010	2011	2012	Total	
Patients receiving antibiotics	557 115	572 869	482 765	404 081	525 915	478 687	405 655	361 351	3 788 438	
Total antibiotic prescriptions in database	1 242 363	1 326 908	1 129 517	928 025	1 139 019	1 013 183	818 014	714 897	7 069 563	
Total antibiotic items in database	1 326 540	1 414 867	1 204 414	990 619	1 213 292	1 076 935	870 423	766 350	1 326 540	
Fluoroquinolone prescriptions	291 316	314 089	280 230	224 325	278 096	247 793	188 125	159 648	1 983 622	
Fluoroquinolone agents prescribed	293 251	316 046	282 219	226 161	280 463	249 928	189 582	160 902	1 998 552	
Average prescription per patient per year ± SD (95% CI)	1.45 ± 0.92 (1.44 – 1.45)	1.46 ± 0.92 (1.45 – 1.46)	1.47 ± 0.93 (1.47 – 1.48)	1.45 ± 0.90 (1.44 – 1.45)	1.41 ± 0.85 (1.41 – 1.42)	1.40 ± 0.833 (1.39 – 1.40)	1.36 ± 0.74 (1.33 – 1.34)	1.31 ± 0.71 (1.31 – 1.32)		
Patients claiming fluoroquinolones, n (%)[a]	201 359 (36.1)	214 990 (37.5)	190 509 (39.5)	154 799(38.3)	196 646 (37.3)	177 481(37.1)	140 754 (34.7)	121 422 (33.6)	1 397 960	
Gender, n (%)[b]										*p* – value
Female	124 193 (61.7)	132 502 (61.6)	117 093 (61.5)	95 366 (61.6)	119 219 (60.6)	107 331 (60.5)	84 458 (60.0)	70 091 (57.7)	850 253	
Male	77 009 (38.2)	82 382 (38.3)	73 380 (38.5)	59 433 (38.4)	77 427 (39.4)	70 150 (39.5)	56 296 (40.0)	51 330 (42.3)	547 407	< 0.0001
Unidentified	157 (0.08)	106 (0.05)	36 (0.02)	-	-	-	-	1 (0.00001)	300	
Age groups, n (%)[b]										
> 18 and ≤ 30 years	28 506 (14.2)	31 842 (14.8)	28 206 (14.8)	20 740 (13.4)	31 918 (16.2)	28 364 (16.0)	22 098 (15.7)	18 931 (15.6)	210 605	
> 30 and ≤ 45 years	71 571 (35.5)	73 872 (34.4)	61 478 (32.3)	45 486 (29.4)	57 319 (29.1)	50 061 (28.2)	39 778 (28.3)	34 613 (28.5)	434 170	< 0.0001
> 45 and ≤ 65 years	69 991 (34.8)	76 594 (35.6)	70 090 (36.8)	61 131 (39.5)	72 644 (36.9)	65 004 (36.6)	51 001 (36.2)	45 087 (37.1)	511 542	
> 65 years	31 291 (15.4)	32 682 (15.2)	30 735 (16.1)	27 442 (17.7)	34 765 (17.7)	34 052 (19.2)	27 877 (19.8)	22 791 (18.8)	241 635	

[a] Percentages were calculated according to the total number of patients claiming antibiotics in each respective year

[b] Percentages were calculated according to the total number of patients claiming fluoroquinolones in each respective year

SD – standard deviation, CI – confidence interval, where $p < 0.0001$, Cramer's $V < 0.5$

Table 2 Average defined daily dose (DDD) per prescription per patient per year of fluoroquinolones prescribed (2005 – 2012)

			Number of fluoroquinolone agents, average DDD ± SD (95% Confidence Interval)								
ATC Code	**Description**		**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	***p* – value***
J01MA06	Norfloxacin	n	22 275	19 238	15 036	11 291	12 145	10 274	8 507	6 560	
		DDD ± SD	3.68 ± 2.75	3.74 ± 2.36	3.67 ± 2.39	3.66 ± 2.51	3.69 ± 1.95	3.79 ± 2.09	3.81 ± 2.25	3.82 ± 2.28	< 0.0001
		95% CI	(3.64 – 3.72)	(3.70 - 3.77)	(3.64 - 3.71)	(3.62 - 3.71)	(3.65 - 3.72)	(3.75 - 3.83)	(3.76 - 3.85)	(3.77 - 3.88)	
J01MA02	Ciprofloxacin	n	151 394	164 354	145 000	116 298	143 955	133 097	102 957	90 860	
		DDD ± SD	4.12 ± 3.21	4.31 ± 6.78	4.47 ± 2.84	4.59 ± 3.10	4.65 ± 2.96	4.71 ± 2.61	4.77 ± 2.29	4.84 ± 2.27	< 0.0001
		95% CI	(4.10 - 4.13)	(4.27 - 4.34)	(4.45 - 4.48)	(4.58 - 4.61)	(4.64 - 4.67)	(4.70 - 4.73)	(4.76 - 4.78)	(4.83 - 4.86)	
J01MA01	Ofloxacin	n	14 861	15 566	11 481	7 606	5 764	3 866	1 852	1 892	
		DDD ± SD	7.22 ± 3.92	7.26 ± 3.53	7.55 ± 3.31	7.39 ± 3.94	7.34 ± 3.75	7.66 ± 5.75	7.63 ± 5.75	7.63 ± 4.57	< 0.0001
		95% CI	(7.16 - 7.28)	(7.20 - 7.31)	(7.49 - 7.61)	(7.30 - 7.48)	(7.24 - 7.43)	(7.48 - 7.84)	(7.37 - 7.89)	(7.43 - 7.84)	
J01MA04	Enoxacin	n	47	50	29	-	-	-	-	-	
		DDD ± SD	4.36 ± 1.64	4.84 ± 6.62	3.60 ± 0.39						0.60
		95% CI	(3.88 - 4.84)	(2.96 - 6.72)	(3.46 - 3.75)						
J01MA14	Levofloxacin	n	40 501	50 065	50 500	46 844	65 698	57 211	41 224	33 127	
		DDD ± SD	5.47 ± 4.57	5.79 ± 3.70	6.15 ± 6.22	6.65 ± 5.90	7.04 ± 5.44	7.23 ± 4.44	7.30 ± 3.33	7.52 ± 3.72	< 0.0001
		95% CI	(5.43 - 5.52)	(5.76 - 5.82)	(6.10 - 6.21)	(6.59 - 6.70)	(7.00 - 7.08)	(7.19 - 7.26)	(7.27 - 7.33)	(7.48 - 7.56)	
J01MA14	Moxifloxacin	n	41 925	50 553	51 046	38 318	46 851	41 335	33 252	27 495	
		DDD ± SD	5.81 ± 4.03	5.89 ± 5.45	5.96 ± 2.76	6.00 ± 1.99	5.91 ± 2.72	5.86 ± 1.90	5.87 ± 2.31	5.90 ± 4.84	< 0.0001
		95% CI	(5.77 - 5.85)	(5.85 - 5.94)	(5.94 - 5.99)	(5.98 - 6.02)	(5.88 - 5.93)	(5.84 - 5.88)	(5.85 - 5.89)	(5.84 - 5.96)	
J01MA16	Gatifloxacin	n	13 031	5 997	154	61	-	-	-	-	
		DDD ± SD	6.90 ± 1.56	6.98 ± 1.79	7.13 ± 1.06	7.05 ± 0.38					0.015
		95% CI	(6.87 - 6.92)	(6.94 - 7.03)	(6.96 - 7.30)	(6.95 - 7.15)					

**p* – values were determined from ANOVA comparing the differences in the average DDD per prescription per patient between the different years.

Where n – number of fluoroquinolone agents; DDD – defined daily dose; SD – standard deviation; and CI – confidence interval

Table 3 Trends in fluoroquinolone use expressed in DDD/1000 inhabitants-days (2005 – 2012)

			DDD/1000 inhabitant-days (DID), n (%)*							
Generation	**ATC Code**	**Description**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**
1st	J01MA06	Norfloxacin	0.17 (6.0)	0.14 (4.6)	0.14 (3.8)	0.13 (3.6)	0.10 (3.0)	0.09 (2.8)	0.09 (3.3)	0.07 (2.9)
2nd	J01MA02	Ciprofloxacin	1.30 (45.8)	1.42 (46.4)	1.70 (45.7)	1.63 (45.7)	1.51 (44.7)	1.48 (46.5)	1.29 (47.6)	1.19 (49.4)
	J01MA04	Enoxacin	0.0004 (0.01)	0.0005 (0.02)	0.0003 (0.01)	-	-	-	-	-
	J01MA14	Levofloxacin	0.46 (16.2)	0.58 (19.0)	0.82 (22.2)	0.95 (26.6)	1.04 (30.8)	0.97 (30.5)	0.79 (29.2)	0.67 (27.6)
	J01MA01	Ofloxacin	0.22 (7.7)	0.23 (7.5)	0.23 (6.2)	0.17 (4.8)	0.10 (3.0)	0.07 (2.2)	0.04 (1.5)	0.04 (1.7)
3rd	J01MA16	Gatifloxacin	0.19 (6.7)	0.08 (2.6)	0.003 (0.1)	0.001 (0.03)	-	-	-	-
	J01MA14	Moxifloxacin	0.51 (18.0)	0.60 (19.6)	0.80 (21.7)	0.70 (19.6)	0.62 (18.3)	0.57 (17.9)	0.51 (18.8)	0.44 (18.3)
	Total		**2.84 (100.0)**	**3.06 (100.0)**	**3.69 (100.0)**	**3.57 (100.0)**	**3.38 (100.0)**	**3.18 (100.0)**	**2.71 (100.0)**	**2.41 (100.0)**

*Percentages were calculated according to the total DID in each respective year

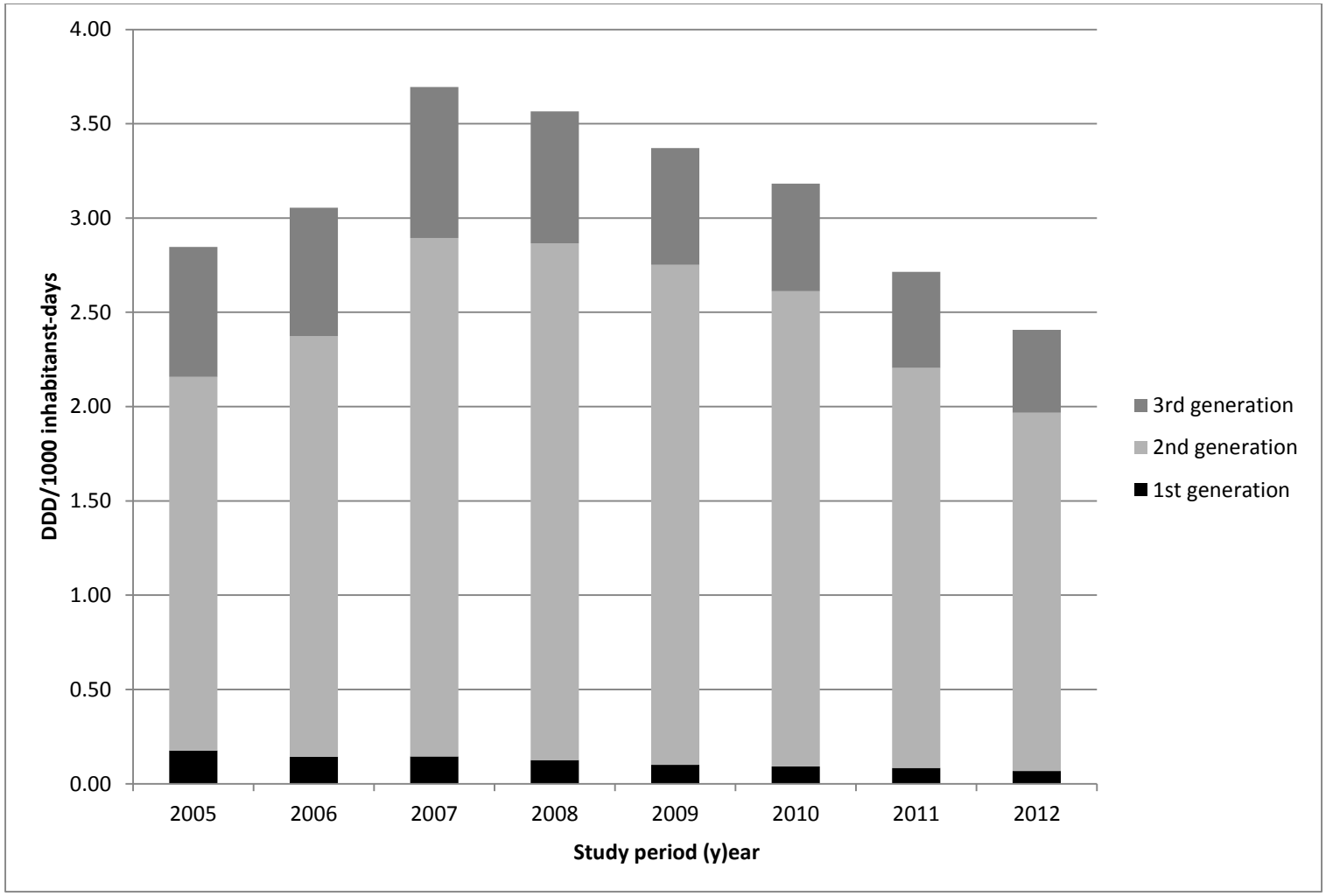

Figure 1 Fluoroquinolone use by generations (2005 – 2012)

3.4 Manuscript three

Prescribing patterns of fluoroquinolones in children and adolescents in the private health sector of South Africa (2005-2012)

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SUMMARY

What is known and objective

The fluoroquinolones represent major clinical advancements; however, their use in patients 18 years and younger has been limited due to associated arthropathy and tendinopathy. There is limited data on fluoroquinolone use in children in South Africa. The aim of this study was to determine the prevalence of fluoroquinolone outpatient prescribing in patients 18 years and younger from 2005 to 2012 in a section of the South African private health sector.

Method

Prescription data on outpatient fluoroquinolone (J01MA) use at the active ingredient level in patients 18 years and younger were collected from a nationally representative prescription claims database from 2005 to 2012. Fluoroquinolone prescribing was analysed based on age groups, gender and prescribers' speciality.

Results

Between 2005 and 2012, a total of 57 325 prescriptions for fluoroquinolones were claimed by the study population. The prevalence of patients receiving at least one fluoroquinolone prescription decreased from 3.6% (n = 8 329) in 2005 to 2.9% (n = 3 310) in 2012. Fluoroquinolones were mostly prescribed to females and to patients between 12 and 18 years ($p < 0.0001$, Cramer's $V < 0.5$ for both trends). Prescribing in all the age groups was mainly done by general medical practitioners ($p < 0.0001$, Cramer's $V \leq 0.30$). In all the age groups, ciprofloxacin was the most prescribed fluoroquinolone, followed by levofloxacin.

What is new and conclusion

Fluoroquinolone prescribing was evident in all age groups during the study period. Overall,

fluoroquinolone prescribing decreased by 0.7% from 2005 to 2012. The specialty of the prescriber was found to influence the prevalence of fluoroquinolone prescribing in all age groups during the study period.

What is known and objective

The use of fluoroquinolones in patients 18 years and younger has raised scepticisms in the field of medicine, limiting their use.[1, 2] Although fluoroquinolones in pre-clinical studies were found to induce changes in the immature articular cartilage of the weight-bearing joints, [3, 4] there have been reports of fluoroquinolone use in paediatric patients.[5, 6] The use of fluoroquinolones in paediatrics has been limited to specific cases where prescribers' judgements on weighing the benefits against the risks are highly crucial.[7] In the United States, more than eight million prescriptions for ciprofloxacin were issued to patients younger than 18 years in 1996.[5] In 2002, 520 000 prescriptions for fluoroquinolones were issued to children, although only ciprofloxacin was approved by the FDA for inhalational anthrax.[6]

Over the past three decades, the favourable clinical outcomes of fluoroquinolones have gradually shifted from 'compassionate use'[8] to 'first-line' drugs in certain clinical conditions.[9] Numerous studies have indicated excellent cure rates with little or no incidence of arthralgia in children.[10-18] In 2006, the Committee on Infectious Diseases (CID) in the United States[6] approved the use of fluoroquinolones in children younger than 18 years in infections caused by multi-drug resistant (MDR) pathogens for which there are no safer and effective alternatives. Fluoroquinolones are also recommended when therapies by parenteral route are not possible and there are no other agents available.[6] Furthermore, fluoroquinolones are approved for the following indications: treatment of inhalational anthrax; urinary-tract infections and chronic pus-producing otitis media or malignant otitis externa caused by *Pseudomonas aeruginosa* or MDR pathogens; life-threatening infections caused by fluoroquinolone-susceptible bacteria in children who are allergic to safer alternate treatments; and documented bacterial septicaemia or meningitis caused by bacteria with *in vitro* resistance to approved therapy.[6]

In South Africa, levofloxacin, moxifloxacin and ofloxacin are second-line agents in the management of MDR tuberculosis; [19, 20] ciprofloxacin is recommended for the treatment of pulmonary exacerbation in cystic fibrosis[21] and gastro-intestinal infections caused by *Shigella*, *Salmonella typhi* and *Vibrio cholerae*.[20] However, little data exist on the use of fluoroquinolone in children and adolescents in clinical practice. The aim of this study was to determine the prevalence of fluoroquinolone prescribing in patients 18 years and younger from 2005 to 2012 in a section of the South African private health sector.

Method

A retrospective drug utilisation study was used to investigate the use of fluoroquinolone agents in patients 18 years and younger in a section of the private health sector of South Africa. The data were obtained from a South African Pharmaceutical Benefit Management (PBM) company. Fluoroquinolones were defined as all active substances belonging to the J01MA classification of the ATC index. The study population comprised 1 366 824 children and adolescents aged 18 years and younger who claimed at least one antibiotic prescription.

Variables

The prevalence of fluoroquinolone prescribing was analysed based on age, gender and prescriber speciality. Patients' ages were determined on the date of the next year following the treatment date and divided into three groups: ≥0 and ≤5 years; >5 and ≤12 years and >12 and ≤18 years. The specialities of prescribers were grouped into five main categories, namely general practitioners, paediatricians, specialists (e.g. oncologists, cardiologists, urologists, neurologists, obstetricians/gynaecologists), pharmacotherapists and others (e.g. dentists and

dermatologists) to determine the prevalence of fluoroquinolone prescribing by prescriber in the different age groups.

Statistical analyses

Basic descriptive statistics were used to describe the study population. Data were analysed using SAS software, version 9.3.[22] Statistically significant results were considered with a probability of $p < 0.05$. The practical significance of results was computed when the *p*-value was statistically significant ($p \leq 0.05$). A two-sample independent *t*-test was used to compare the average number of fluoroquinolone prescriptions per patient per year by gender. The chi-square test (χ^2) was used to determine the association between the prevalence of fluoroquinolone prescriptions and gender; between the different age groups; and the prescribers' specialty stratified by the study period. Cramer's *V* statistic was used to test the practical significance of these associations (with Cramer's $V \geq 0.5$ defined as practically significant).

Ethics

This study was approved by the Ethics Committee of the North-West University (NWU-0046-08-550) and the board of directors of the South African Pharmaceutical Benefit Management Company (PBM). Data privacy and confidentiality were maintained at all times; therefore, no patient or medical scheme/administrator could be traced. Additionally, it was not possible to determine which prescribers or providers (i.e. name of the prescriber/provider) were involved in the prescribing/dispensing of the medicine items. The PBM providing the data for the study is furthermore nowhere identified in this study. The researcher, study promoter and co-promoter furthermore signed confidentiality agreements.

Results

Fluoroquinolone use by study population

A total of 49 540 patients, 18 years and younger, received at least one prescription for a fluoroquinolone during the study period, representing 3.6% of the total number of patients claiming antibiotic prescriptions (Table 1). The percentage of patients receiving fluoroquinolone prescriptions decreased from 3.6% (n = 8 329) in 2005 to 2.9% (n = 3 310) in 2012; however, peaking at 4.4% (n = 5 697) in 2008 (Table 1). Overall, 57 325 fluoroquinolone prescriptions and 57 593 fluoroquinolone items were claimed. The average number of fluoroquinolone prescriptions per patient per year ranged from 1.17 ± 0.53 (95% CI 1.16-1.18) in 2005 to 1.12 ± 0.42 (95% CI 1.10-1.13) in 2012. The average number of fluoroquinolone items per prescription per year remained fairly constant at 1.01 ± 0.07 (95% CI 1.00-1.01) in 2005 through to 1.00 ± 0.06 (95% CI 1.00-1.01) in 2012.

The prevalence of fluoroquinolone prescriptions was higher in females, ranging from 56.3% (n = 4 690) in 2005 to 55.8% (n = 1 848) in 2012. The highest prevalence of patients receiving fluoroquinolone prescriptions was observed in patients between 12 and 18 years, ranging from 80.5% (n = 6 706) in 2005 to 79.5% (n = 2 631) in 2005. The lowest prevalence was observed in patients five years and younger; however, increasing from 3.1% (n = 261) to 5.3% (n = 175) in 2012 (Table 1). No practically significant association was found between the prevalence of patients claiming fluoroquinolone prescriptions by gender ($p < 0.0001$, Cramer's $V = 0.03$) and in the different age groups ($p < 0.0001$, Cramer's $V = 0.04$) during the study period.

See table 1

Fluoroquinolones prescribed in the different age groups

In patients five years and younger, a total of 1 907 fluoroquinolone items were prescribed. Ciprofloxacin accounted for 87% (n = 1 653) of fluoroquinolones prescribed in this age group, followed by levofloxacin, representing 8.4% (n = 160) of the total number of fluoroquinolones prescribed. Moxifloxacin represented 2.1% (n = 41). Gatifloxacin, gemifloxacin, lomefloxacin, norfloxacin and ofloxacin represented less than 3% of the total fluoroquinolones prescribed (Table 2).

A total of 7 987 fluoroquinolone items were prescribed in patients between five and 12 years during the study period. Again, ciprofloxacin was the most prescribed fluoroquinolone, accounting for 71.7% (n = 5 724) of all fluoroquinolones prescribed in this age group, followed by levofloxacin and moxifloxacin, representing 7.3% (n = 160) and 7.2% (n = 577), respectively. Ofloxacin and norfloxacin accounted for 6.7% (n = 536) and 4.5% (n = 359) of the total number of fluoroquinolones prescribed during the study period (Table 2).

Patients between 12 and 18 years claimed a total of 47 696 fluoroquinolones. Again, ciprofloxacin was the most prescribed fluoroquinolone representing 62.5% (n = 29 822) of fluoroquinolones prescribed in this age group. This was followed by levofloxacin and moxifloxacin, representing 11.9% (n = 5 659) and 11.5% (n = 5 484), respectively. Ofloxacin and norfloxacin accounted for 5.6% (n = 2 694) and 5.0% (n = 2 374) of the total number of fluoroquinolones prescribed, respectively. Gemifloxacin accounted for 2.8% (n = 1 322) of the total number of fluoroquinolones prescribed. Gatifloxacin, lomefloxacin and enoxacin represented less than 1% of the total number of fluoroquinolones prescribed.

See table 2

Fluoroquinolones by prescribers' speciality

General medical practitioners prescribed the most fluoroquinolones during the study period in all the age groups compared to paediatricians (Table 3). The least prescribing throughout the study period was by pharmacotherapists. Though statistically significant, there was no practical association between the number of fluoroquinolone prescribed and the type of prescriber in the different age groups during the study period ($p < 0.0001$, Cramer's $V \leq 0.30$).

See table 3

Discussion

Fluoroquinolone prescribing was most prevalent in patients between 12 and 18 years. Most fluoroquinolone prescribing was by general medical practitioners in the different age groups. Ciprofloxacin was the most prescribed fluoroquinolone in all the different age groups during the study period. In this study, we observed that fluoroquinolone prescribing in patients 18 years and younger generally decreased over the study period.

The high prescription rate by general medical practitioners can be accounted for by the higher proportion of general medical practitioners than other prescribers in the private health sector of South Africa;[23] therefore, patients are more likely to be attended to by a general medical practitioner.

Ciprofloxacin was the most prescribed fluoroquinolone in all the age groups. This finding confirms reports from the United States of America[5, 6] and France.[24] Our findings may be as a result of ciprofloxacin being the only fluoroquinolone approved for several indications in the paediatric population of South Africa.[20, 21] Ciprofloxacin is recommended for the treatment of

salmonella, *Shigella* and *Vibrio cholerae* infections in children.[20, 25-29] Diarrhoeal diseases of bacterial origin accounted for 8% of deaths in 2012.[30] In 2005, an outbreak of *Salmonella typi* infection with the highest prevalence in children from birth to 19 years occurred in South Africa.[31, 32] Molecular analyses revealed that strains from an earlier epidemic in 1993 were the same as that which occurred in 2005 and a few subsequent cases in 2007 and 2009.[31] *Salmonella typhi* infections and shigellosis are still prevalent in South Africa and with more than 95% of strains susceptible to ciprofloxacin, [33] it is the drug of choice for the treatment in this age group. [20, 25-29] A possible reason for the decrease in ciprofloxacin use during the study period may be attributed to the decrease in the incidence of *Salmonella typhi* infections from 2006[34] to 2012.[35] Furthermore, *Shigella* infection rates decreased from 2.2 cases per 100 000 in 2006[34] to 0.07 cases per 100 000 in 2012.[35] An outbreak of cholera that occurred between November 2008 and April 2009 in South Africa[36] may account for the observed increase in the use of ciprofloxacin within this period, as ciprofloxacin is the first-line drug in managing cholera in South Africa in paediatrics.[20]

Ciprofloxacin is also approved in children for chemoprophylaxis of meningococcal diseases of bacterial origin in close contact with cases.[20, 37] The estimated incidence of meningococcal meningitis in Africa is 38 cases per 100 000, compared to six cases per 100 000 in Europe.[38] Although South Africa is not in the meningitis belt, there have been sporadic cases of the disease occurring mostly during late winter and early spring.[36, 39] High prevalence rates have been reported in children younger than five years and young adults.[39] In 2007, meningococcal meningitis was a major cause of mortality in children younger than four years.[40] The incidence rate of meningococcal diseases has, however, decreased from 1.16 cases per 100 000 in 2005[34] to 0.44 cases per 100 000 in 2012 with the introduction of vaccination.[35] This trend may also further explain the general decrease in ciprofloxacin use over the study period.

Levofloxacin, moxifloxacin and ofloxacin are recommended for use in the treatment of MDR-TB.[19, 20, 41] However, the majority of tuberculosis cases in South Africa are managed in the public sector. The use of fluoroquinolones in the private sector cannot be accounted for as data regarding diagnoses were incomplete.

Our findings further revealed the prescribing of norfloxacin, enoxacin, gemifloxacin, lomefloxacin and gatifloxacin, which have no approved indications in children by the Department of Health of South Africa. The reasons for their use are not known as data concerning diagnoses were incomplete.

A limitation to this study was the inability to correlate fluoroquinolone use with diagnoses as data on diagnoses were not complete. Additionally, the data used represent only a section of patients registered as beneficiaries of medical schemes in South Africa. However, to the best of our knowledge, this is the first study to be conducted measuring fluoroquinolone use and the influence of prescribers in patients 18 years and younger utilising medicine claims data in South Africa. The South African private health sector has coverage of approximately 20% of the country's population, especially for those in employment.

What is new and conclusion

Overall, the prescribing of fluoroquinolones generally decreased over the study period. The findings from this study revealed the use of some fluoroquinolones that are not approved in this patient group. The specialities of prescribers influenced the prevalence of fluoroquinolone prescribing in the different age groups. The use of fluoroquinolones is justified in certain clinical conditions in this patient group; however, appropriate prescribing is crucial in limiting

resistance.

We recommend that further studies be conducted to link fluoroquinolone use with diagnoses to evaluate the appropriateness of prescribing. Furthermore, further studies should be conducted to determine the indications of use of fluoroquinolones with unapproved indications in South Africa.

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Transparency declaration

None to declare.

Authors' contribution

WEA was responsible for the planning and design of the manuscript, the statistical analysis, interpretation of results and writing of the manuscript. MSL supervised the concept of the study and manuscript, the statistical analysis, supervision on writing of the manuscript, and reviewing the manuscript carefully for final approval. JRB and NLK co-supervised the study and manuscript, the data and statistical analyses, supervision of manuscript, and reviewing the manuscript carefully for final approval. MC mainly supervised the statistical analyses.

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Table 1 Demographic distribution of the study population (2005-2012)

Study period	2005	2006	2007	2008	2009	2010	2011	2012	Total	
Patients claiming antibiotics	232 132	230 546	181 709	129 253	183 393	158 446	132 537	118 808	1 366 824	
Total antibiotic prescriptions	510 416	522 769	417 511	286 086	408 702	345 758	269 039	237 023	2 997 304	
Patients claiming fluoroquinolones, n (%)*	8 329 (3.6)	8 901 (3.7)	7 799 (4.3)	5 697 (4.4)	6 571 (3.6)	5 225 (3.3)	3 708 (2.8)	3 310 (2.9)	49 540 (3.6)	
Fluoroquinolone prescriptions, n (%) **	9 741 (1.9)	10 305 (2.0)	9 105 (2.2)	6 654 (2.3)	7 659 (1.9)	6 019 (1.7)	4 144 (1.5)	3 698 (1.6)	57 325	
Gender, n (%) ***										***p* – value [a]**
Female	4 690 (56.3)	4 942 (55.5)	4 343 (55.7)	3 169 (55.6)	3 678 (56.0)	2 911 (55.7)	2 093 (56.5)	1 848 (55.8)	27 674	
Male	3 618 (43.4)	3 951 (44.8)	3 452 (44.2)	2 528 (44.4)	2 893 (44.0)	2 314 (44.3)	1 615 (43.5)	1 462 (44.2)	21 833	< 0.0001
Unidentified	21 (0.3)	8 (0.1)	4 (0.1)	-	-	-	-	-	33	
Age group (years) n (%)**										
≥ 0 and ≤ 5	261 (3.1)	283 (3.2)	242 (3.1)	130 (2.3)	252 (3.8)	246 (4.7)	190 (5.1)	175 (5.3)	1 779	
> 5 and ≤ 12	1 362 (16.4)	1 376 (15.4)	1 116 (14.3)	777 (13.6)	911 (13.9)	673 (12.9)	512 (13.8)	504 (15.2)	7 231	< 0.0001
> 12 and ≤ 18	6 706 (80.5)	7 242 (81.4)	6 441 (82.6)	4 790 (84.1)	5 408 (82.3)	4 306 (82.4)	2 631 (81.1)	2 631 (79.5)	40 530	

* Percentages were calculated according to the total number of patients receiving antibiotic prescriptions.

** Percentages were calculated according to the total number of antibiotic prescriptions in each year.

*** Percentages were calculated according to the total number of patients receiving fluoroquinolone prescriptions.

[a] *p*-values were determined from chi-square tests to determine the association that exists between the prevalence of patients receiving fluoroquinolone prescriptions and the study period.

Table 2 Frequency of fluoroquinolones prescribed during the study period stratified by age groups

Age groups (years)	Fluoroquinolone	Number of fluoroquinolones, n (%)* 2005	2006	2007	2008	2009	2010	2011	2012	*p*-value [b]
≥ 0, ≤ 5	Ciprofloxacin	211 (77.0)	268 (87.9)	241 (87.6)	123 (88.5)	243 (91.0)	235 (87.7)	178 (90.0)	154 (85.1)	< 0.0001
	Levofloxacin	29 (10.6)	23 (7.5)	24 (8.7)	14 (10.1)	21 (7.9)	24 (9.0)	16 (8.1)	9 (5.0)	
	Gatifloxacin	11 (4.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0	0 (0.0)	0 (0.0)	
	Moxifloxacin	9 (3.3)	7 (2.3)	2 (0.7)	0 (0.0)	2 (0.7)	8 (2.9)	2 (0.0)	11 (6.1)	
	Norfloxacin	8 (2.9)	2 (0.7)	5 (1.8)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	3 (1.7)	
	Ofloxacin	4 (1.4)	4 (1.3)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.7)	
	Gemifloxacin	1 (0.4)	0 (0.0)	3 (1.1)	1 (0.7)	1 (0.4)	0 (0.0)	2 (1.0)	1 (0.6)	
	Lomefloxacin	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Enoxacin	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Total	**274 (100.0)**	**305 (100.0)**	**275 (100.0)**	**139 (100.0)**	**267 (100.0)**	**268 (100.0)**	**198 (100.0)**	**181 (100.0)**	
> 5, ≤ 12	Ciprofloxacin	968 (62.9)	997 (66.2)	893 (73.0)	611 (71.4)	764 (75.2)	577 (78.3)	445 (81.8)	469 (86.3)	<0.0001
	Ofloxacin	231 (15.0)	136 (9.0)	75 (6.0)	36 (4.2)	20 (2.0)	23 (3.1)	11 (2.0)	4 (0.7)	
	Moxifloxacin	103 (6.7)	117 (7.8)	104 (8.4)	59 (6.9)	79 (7.8)	53 (7.2)	38 (7.0)	25 (4.4)	
	Levofloxacin	92 (6.0)	123 (8.2)	78 (6.3)	75 (8.8)	105 (10.3)	52 (7.1)	24 (4.4)	38 (6.9)	
	Norfloxacin	86 (5.6)	81 (5.4)	50 (4.0)	55 (6.4)	32 (3.1)	27 (3.7)	16 (2.9)	12 (2.2)	
	Gatifloxacin	27 (1.8)	16 (1.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Gemifloxacin	27 (1.8)	30 (2.0)	39 (3.1)	20 (2.3)	16 (1.6)	5 (0.7)	2 (0.4)	4 (0.7)	
	Lomefloxacin	4 (0.3)	5 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Enoxacin	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Total	**1 538 (100.0)**	**1 506 (100.0)**	**1 240 (100)**	**856 (100.0)**	**1 016 (100.0)**	**737 (100.0)**	**544 (100.0)**	**550 (100.0)**	
> 12, ≤ 18	Ciprofloxacin	4 691 (58.7)	5 071 (59.5)	4 705 (61.7)	3 499 (61.5)	4 005 (62.4)	3 370 (66.7)	2 384 (69.8)	2 097 (70.3)	< 0.0001
	Moxifloxacin	782 (9.8)	989 (11.6)	1009 (13.2)	715 (12.6)	716 (11.2)	560 (11.1)	375 (11.0)	338 (11.3)	
	Ofloxacin	761 (9.5)	630 (7.4)	373 (4.9)	262 (4.3)	170 (2.6)	109 (2.2)	36 (1.0)	33 (1.1)	
	Levofloxacin	732 (9.2)	904 (10.6)	799 (10.5)	709 (12.4)	1037 (16.2)	682 (13.5)	416 (12.2)	380 (12.7)	
	Norfloxacin	620 (7.8)	556 (6.5)	434 (6.7)	315 (5.5)	292 (4.5)	199 (3.9)	167 (4.9)	111 (3.7)	
	Gemifloxacin	217 (2.7)	247 (2.9)	292 (3.8)	186 (3.3)	189 (2.9)	128 (2.5)	38 (1.1)	25 (0.8)	
	Gatifloxacin	167 (2.1)	97 (1.1)	9 (0.1)	1 (0.02)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Lomefloxacin	15 (0.2)	32 (0.4)	6 (0.1)	6 (0.1)	6 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	
	Enoxacin	0 (0.0)	1 (0.01)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Total	**7 985 (100.0)**	**8 527(100.0)**	**7 627 (100.0)**	**5 693 (100.0)**	**6 415 (100.0)**	**5 049 (100.0)**	**3 416 (100.0)**	**2 984 (100.0)**	

*Percentages were calculated according to the total number of fluoroquinolones prescribed in each age group per year.

[b] *p*-values were determined from chi-square test to determine the association that exists between the prevalence of fluoroquinolones prescribed and the study period stratified by age groups.

Table 3 Total fluoroquinolones prescribed by prescriber specialty during the study period stratified by age groups

			Number of fluoroquinolones, n (%)*					
Year	**Age groups (years)**	**Total fluoroquinolones prescribed (N)**	**General medical practice**	**Paediatrician**	**Specialist**	**Pharmacotherapist**	**Other**	***p*-value [c]**
2005	**≥ 0, ≤ 5**	274	199 (72.6)	50 (18.2)	4 (1.5)	4 (1.5)	17 (6.2)	
	> 5, ≤ 12	1 538	1 399 (91.0)	63 (4.1)	15 (1.0)	1 (0.01)	60 (3.9)	< 0.0001
	> 12, ≤ 18	7 985	7 554 (94.6)	66 (0.8)	88 (1.1)	4 (0.1)	273 (3.4)	
2006	**≥ 0, ≤ 5**	305	217 (71.2)	67 (22.0)	4 (1.3)	0 (0.0)	17 (5.6)	
	> 5, ≤ 12	1 506	1 365 (90.6)	65 (4.3)	17 (1.1)	1 (0.1)	58 (3.3)	< 0.0001
	> 12, ≤ 18	8 527	8 058 (94.5)	84 (1.0)	86 (1.0)	3 (0.04)	296 (3.5)	
2007	**≥ 0, ≤ 5**	275	185 (67.3)	73 (26.5)	3 (1.1)	0 (0.0)	14 (5.1)	
	> 5, ≤ 12	1 240	1 118 (90.2)	60 (4.8)	13 (1.1)	0 (0.0)	49 (3.9)	< 0.0001
	> 12, ≤ 18	7 627	7 206 (94.5)	68 (0.9)	92 (1.2)	1 (0.01)	260 (3.4)	
2008	**≥ 0, ≤ 5**	139	88 (63.3)	37 (26.6)	2 (1.4)	0 (0.0)	12 (8.6)	
	> 5, ≤ 12	856	745 (87.0)	60 (7.0)	13 (1.5)	0 (0.0)	38 (4.4)	< 0.0001
	> 12, ≤ 18	5 693	5 359 (94.1)	59 (1.0)	63 (1.1)	1 (0.02)	211 (3.7)	
2009	**≥ 0, ≤ 5**	267	143 (53.6)	97 (36.3)	2 (0.7)	0 (0.0)	25 (9.4)	
	> 5, ≤ 12	1 016	864 (85.0)	101 (9.9)	6 (0.6)	0 (0.0)	45 (4.4)	< 0.0001
	> 12, ≤ 18	6 415	5 973 (93.1)	83 (1.3)	92 (1.4)	0 (0.0)	267 (4.2)	
2010	**≥ 0, ≤ 5**	268	123 (45.9)	115 (42.9)	4 (4.3)	0 (0.0)	26 (9.7)	
	> 5, ≤ 12	737	614 (83.3)	77 (10.4)	11 (1.5)	0 (0.0)	35 (4.7)	< 0.0001
	> 12, ≤ 18	5 049	4 679 (92.7)	64 (1.3)	79 (1.6)	0 (0.0)	227 (4.5)	
2011	**≥ 0, ≤ 5**	198	104 (52.5)	80 (40.4)	3 (1.5)	0 (0.0)	11 (5.6)	
	> 5, ≤ 12	544	472 (86.8)	43 (7.9)	8 (1.5)	0 (0.0)	21 (3.9)	< 0.0001
	> 12, ≤ 18	3 416	3 179 (93.1)	42 (1.2)	46 (1.3)	0 (0.0)	149 (4.4)	
2012	**≥ 0, ≤ 5**	181	106 (58.6)	64 (35.4)	1 (0.5)	0 (0.0)	10 (5.5)	
	> 5, ≤ 12	550	468 (85.1)	55 (10.0)	7 (1.3)	0 (0.0)	20 (3.6)	< 0.0001
	> 12, ≤ 18	2 984	2 782 (93.2)	38 (1.3)	30 (1.0)	0 (0.0)	134 (4.5)	

*Percentages were calculated according to the total number of fluoroquinolones prescribed in each age group (N).

[c] Chi square test was used to determine the association that exists between the prevalence of fluoroquinolones prescribed and the type of prescriber in the different age groups.

3.5 Additional results

The subsequent paragraphs and Tables 3.1 - 3.2 provide additional results which were obtained from the empirical investigation.

3.5.1 PDDs of fluoroquinolones stratified by age groups

In Table 3.1, the PDDs (average dose) of fluoroquinolones prescribed for children and adolescents stratified by age groups are provided. With reference to the maximum recommended daily doses determined from literature for each fluoroquinolone in Table 1.4, the following observations were made:

- The PDDs and the maximum prescribed doses of gatifloxacin, lomefloxacin, moxifloxacin and ofloxacin exceeded the maximum recommended daily dose in patients from birth to five years in 2005.
- The maximum prescribed doses and PDDs of gatifloxacin, gemifloxacin, lomefloxacin, moxifloxacin, norfloxacin and ofloxacin exceeded the maximum recommended daily dose in children above five to 12 years in 2005 and 2006.
- In children above 12 to 18 years, the maximum recommended daily doses of gatifloxacin, gemifloxacin, lomefloxacin, ofloxacin, moxifloxacin and norfloxacin were exceeded in 2005 and 2006 with regard to the PDDs and maximum prescribed doses.
- All PDDs of ciprofloxacin in all the age groups were below the maximum recommended daily dose. There were, however, wide variations around the PDDs as shown by the minimum and maximum doses prescribed. In all the age groups, the maximum doses prescribed exceeded the maximum recommended daily dose (1 500 mg) throughout the study period.
- Enoxacin was only prescribed in children above five to 18 years in 2006. The PDD was below the maximum recommended daily dose (refer to Table 1.4).
- The PDDs of levofloxacin in all the age groups were below the maximum recommended daily dose. Again, wide variations around the PDDs were observed. The maximum doses prescribed for children from birth to five years and in children above 12 to 18 years, exceeded the maximum recommended daily dose in 2005 (refer to Table 3.1). In children above five to 12 years, maximum prescribed doses exceeded the maximum recommended daily dose in 2005 and 2006 (refer to Table 3.1).

Practically significant differences were found in the average PPDs between 2005 and the

subsequent years under study for norfloxacin in children above five to twelve years (Cohen's *d*-value ≥ 0.84); between 2006 and 2010 (Cohen's *d*-value = 0.83) and between 2006 and 2011 (Cohen's *d*-value = 1.04) in patients above twelve to 18 years.

For ofloxacin, practically significant differences were found in the average PPDs between 2005 and the subsequent years in patients above five to twelve years (Cohen's *d*- value ≥ 0.80); between 2006 and 2010, 2011, 2012 (Cohen's *d*-value ≥1.43); and between 2007 and 2010, 2012 (Cohen's *d*-value ≥ 0.87). Again, the same trend was found between 2008 and 2010, 2012 (Cohen's *d*-value ≥ 0.82); and between 2009 and 2012 in this age group (Cohen's *d*-value = 1.03). In patients above five to twelve years, practically significant differences were found in the average PPDs between 2005 and the other years under study (Cohen's *d*-value ≥ 1.16); and between 2006 and 2010 (Cohen's *d*-value = 0.87).

Lastly for norfloxacin, practically significant differences were observed in the differences in the average PPDs between 2005 and the other years under study (Cohen's *d*-value ≥ 0.88). High dosages prescribed during the study period may reflect uncertaities in dosages or prescribing guidelines. The appropriateness of dosages prescribed could not be evaluated due to incomplete diagnoses data and relevant data fields such as the weight and height of patients.

3.5.2 PDDs of fluoroquinolones by prescribers' specialty

Table 3.2 provides the PDDs of fluoroquinolones by prescribers' specialty. General medical practitioners were accountable for relative higher average PDDs prescribed for all fluoroquinolones claimed. In 2007, general medical practitioners prescribed higher average PDDs of ciprofloxacin than pharmacotherapist (Cohen's *d*-value = 1.24). PDDs for ofloxacin were observed to be higher in general medical practitioners than the rest of the prescribers in 2005 (Cohen's *d*-value ≥ 1.41) and in 2006 (Cohen's *d*-value ≥ 0.80). Again in 2007, PDDs by general medical practitioners differed significantly from other prescribers (Cohen's *d*-value = 1.01) and between the specialists and other prescribers (Cohen's *d*-value = 1.63). In 2009, high PDDs were observed in general medical practitioners compared to paediatricians (Cohen's *d*-value = 2.49); between the specialists and paediatricians (Cohen's *d*-value = 3.05); and between paediatricians and other prescribers (Cohen's *d*-value = 2.38). Finally in 2010, the differences in the PDDs between the general medical practitioners and paediatricians was found to be practically significant (Cohen's *d*-value = 1.59); as well as that between the specialists and paediatricians (Cohen's *d*-value = 1.67). Dosing of

fluoroquinolones in children is essential to achieve the desired therapeutics effects and limit resistance (Alghasham & Nahata, 2000:348). Although high doses prescribed for fluoroquinolones were observed by general medical practitioners, they could not be explored further to draw satisfactory conclusions as data for diagnoses were incomplete.

Table 3.1 Prescribed daily doses per prescription per year stratified by age groups

		≥0, ≤5 years								
FQ		**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	***p* - value**
Ciprofloxacin	n PDD ± SD 95% CI Min. Max. Med.	211 1 062.47 ± 787.44 (955.61 – 1 169.34) 57.14 2 500.00 1 000.00	268 910.13 ± 592.80 (838.83 - 981.43) 125.00 3 750.00 885.42	241 722.13 ± 409.50 (670.17 - 774.09) 28.57 2 500.00 625.00	123 776.83 ± 336.21 (716.81 - 836.84) 166.67 1 666.67 750	243 821.22 ± 390.02 (771.93 - 870.50) 142.86 2 500.00 750.00	235 818.93 ± 507.16 (753.75 - 884.11) 125.00 2 000.00 1 000.00	178 814.17 ± 344.53 (763.21 - 865.13) 40.00 1 666.67 1 000.00	154 769.06 ± 296.86 (721.80 - 816.31) 166.67 1 666.67 1 000.00	0.0001
Enoxacin		-	-	-	-	-	-	-	-	-
Gatifloxacin	n PDD ± SD 95% CI Min. Max. Med.	11 436.36 ± 332.48 (213.00 - 659.73) 200.00 1400.00 400.00	1 400.00 ± 0.00 - 400.00 400.00 400.00	-	-	-	-	-	-	0.920
Gemifloxacin	n PDD ± SD 95% CI Min. Max. Med.	1 320.00 ± 0.00 - 320.00 320.00 320.00	-	3 320.00 ± 0.00 - 320.00 320.00 320.00	1 320.00 ± 00 - 320.00 320.00 320.00	1 320.00 ± 0.00 - 320.00 320.00 320.00	-	2 320.00 ± 0.00 - 320.00 320.00 320.00	1 320.00 ± 0.00 - 320.00 320.00 320.00	-
Levofloxacin	n PDD ± SD 95% CI Min. Max. Med.	29 586.21 ± 445.84 (416.62 - 755.80) 250.00 2 500.00 500.00	23 481.88 ± 115.02 (432.14 - 531.62) 250.00 833.33 500.00	24 508.68 ± 156.38 (442.65 - 574.71) 250.00 1 000.00 500.00	14 642.86 ± 212.91 (519.93 - 765.79) 142.86 1 000.00 500.00	21 572.28 ± 282.49 (443.69 - 700.87) 142.86 1 000.00 500.00	24 677.08 ± 280.52 (558.63 - 795.54) 250.00 1 000.00 500.00	16 492.19 ± 132.83 (421.41 - 562.97) 250.00 750.00 500.00	9 722.22 ± 291.67 (498.03 - 946.42) 250.00 1 000.00 750.00	0.10
Lomefloxacin	n PDD ± SD	1 1000.00 ± 0.00	-	-	-	-	-	-	-	-

Table 3.1 Prescribed daily doses per prescription per year stratified by age groups (continued)

		≥0, ≤5 years								
FQ		**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	***p* - value**
Moxifloxacin	n PDD ± SD 95% CI Min. Max. Med.	9 466.67 ± 200.00 (312.93 – 620.00) 400.00 1 000.00 400.00	7 400 ± 0.00 - 400.00 400.00 400.00	2 300.00 ± 141.92 (-970.62 – 1 570.62) 200.00 400.00 300.00	-	2 400.00 ± 0.00 - 400.00 400.00 400.00	8 350.00 ± 92.58 (272.60 – 427.40) 200.00 400.00 400.00	2 400.00 ± 0.00 - 400.00 400.00 400.00	11 400.00 ± 0.00 - 400.00 400.00 400.00	0.36
Norfloxacin	n PDD ± SD 95% CI Min. Max. Med.	8 760.00 ± 375.23 (446.30 - 1073.70) 80.00 1200.00 800.00	2 800.00 ± 0.00 - 800.00 800.00 800.00	5 720.00 ± 178.89 (497.88 - 942.12) 400.00 800.00 800.00	-	-	1 800.00 ± 0.00 - 800.00 800.00 800.00	-	3 800.00 ± 0.00 - 800.00 800.00 800.00	0.99
Ofloxacin	n PDD ± SD 95% CI Min. Max. Med.	4 1 250.00 ± 525.99 (413.03 – 2 086.97) 800.00 2 000.00 1 100.00	4 700.00 ± 346.41 (148.78 – 1 251.22) 200.00 1 000.00 800.00	-	1 800.00 ± 0.00 - 800.00 800.00 800.00	-	-	-	3 600.00 ±346.41 (-260.53 - 1460.53) 200.00 800.00 800.00	0.24

Table 3.1 Prescribed daily doses per prescription per year stratified by age groups (continued)

		>5, ≤12 years								
FQ		**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	***p* - value**
Ciprofloxacin	n PDD ± SD 95% CI Min. Max. Med.	968 1 223.55 ± 578.64 (1 123.98 – 1 323.12) 16.67 5 000.00 1 000.00	997 1 009.23 ± 693.44 (966.13 – 1 052.32) 33.33 5 000.00 1 000.00	893 858.88 ± 404.75 (832.30 - 885.46) 125.00 1 666.67 833.33	611 886.08 ± 402.09 (854.13 - 918.02) 166.67 2 000.00 1 000.00	764 1 004.52 ± 2 893.16 (798.91 - 1210.13) 25.00 2 000.00 1 000.00	577 843.52 ± 392.40 (811.43 - 875.60) 125.00 2 000.00 833.33	445 851.81 ± 413.38 (813.30 - 890.32) 83.33 3 333.33 1 000.00	469 872.01 ± 366.48 (838.76 - 905.26) 16.67 1 875.00 1 000.00	0.0001
Enoxacin	n PDD ± SD 95% CI Min. Max. Med.	-	1 400.00 ± 0.00 - 400.00 400.00 400.00	-	-	-	-	-	-	.-
Gatifloxacin	n PDD ± SD 95% CI Min. Max. Med.	27 414.81 ± 207.00 (332.93 - 496.70) 200.00 1 400.00 400.00	16 442.50 ± 261.47 (303.17 - 581.83) 200.00 1 400.00 400.00	1 400.00 ± 0.00 - 400.00 400.00 400.00	-	-	-	-	-	0.92
Gemifloxacin	n PDD ± SD 95% CI Min. Max. Med.	27 399.01 ± 201.39 (319.34 - 478.68) 53.33 800.00 320.00	30 352.71 ± 196.30 (279.41 - 426.01) 53.33 800.00 320.00	39 307.69 ± 53.98 (290.19 - 325.19) 53.33 320.00 320.0	20 320.00 ± 0.00 - 320.00 320.00 320.00	16 320.00 ± 0.00 - 320.00 320.00 320.00	5 320.00 ± 0.00 - 320.00 320.00 320.00	2 320.00 ± 0.00 - 320.00 320.00 320.00	4 320.00 ± 0.00 - 320.00 320.00 320.00	0.24
Levofloxacin	n PDD ± SD 95% CI Min. Max. Med.	92 548.73 ± 491.54 (446.94 - 650.53) 83.33 2 500.00 500.00	123 469.50 ± 202.02 (433.44 - 505.56) 250.00 1 250.00 500.00	78 511.75 ± 256.14 (454.00 - 569.50) 166.67 1 000.00 500.00	75 542.78 ± 234.70 (488.78 - 596.78) 125.00 1 000.00 500.00	105 546.11 ± 236.04 (500.43 - 591.79) 83.33 1 000.00 500.00	52 367.38 ± 135.62 (329.62 - 405.13) 50.00 500.00 375.00	24 448.53 ± 213.46 (374.05 - 523.01) 125.00 1 000.00 500.00	38 389.25 ± 119.15 (350.09 - 428.42) 250.00 500.00 458.33	0.0002
Lomefloxacin	n PDD ± SD 95% CI Min. Max. Med.	4 900.00 ± 808.29 (-386.17 - 2186.17) 2..022 2 000.00 700.00	5 960.00 ± 654.22 (147.68 - 1772.32) 400.00 2 000.00 1 000.00	-	-	-	-	-	-	0.91

Table 3.1 Prescribed daily doses per prescription per year stratified by age groups (continued)

		>5, ≤12 years								
FQ		**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	***p* - value**
Moxifloxacin	n	103	117	104	59	79	53	38	24	0.02
	PDD ± SD	474.62 ± 246.18	449.00 ± 356.48	392.67 ± 40.82	400.00 ± 0.00	391.39 ± 45.59	391.95 ± 42.35	396.99 ± 18.54	400.00 ± 0.00	
	95% CI	(426.50 - 522.73)	(383.73 - 514.28)	(384.73 - 400.61)	-	(381.18 - 401.60)	(380.28 - 403.62)	(390.90 - 403.09)	-	
	Min.	66.67	66.67	66.67	400.00	80.00	133.33	285.71	400.00	
	Max.	2 000.00	2 000.00	400.00	400.00	400.00	400.00	400.00	400.00	
	Med.	400.00	400.00	400.00	400.00	400.00	400.00	400.00	400.00	
Norfloxacin	n	86	81	50	55	32	27	16	12	0.0001
	PDD ± SD	985.74 ± 316.99	898.27 ± 308.68	784.80 ± 129.52	761.45 ± 126.25	760.00 ± 130.11	699.26 ± 198.88	647.50 ± 211.77	766.67 ± 115.47	
	95% CI	(917.77 - 1053.70)	(830.02 - 966.53)	(747.99 - 821.61)	(727.32 - 795.58)	(713.09 - 806.91)	(620.58 - 777.93)	(534.66 - 760.34)	(693.30 - 840.03)	
	Min.	160.00	200.00	200.00	200.00	240.00	200.00	200.00	400.00	
	Max.	2 000.00	2 400.00	1 200.00	800.00	800.00	800.00	800.00	800.00	
	Med.	1 200.00	800.00	800.00	800.00	800.00	800.00	800.00	800.00	
Ofloxacin	n	231	136	75	36	20	23	11	4	0.0001
	PDD ± SD	1 214.37 ± 503.09	912.49 ± 375.63	689.96 ± 144.51	669.44 ± 145.71	656.00 ± 209.55	347.83 ± 227.38	436.36 ± 196.33	250.00 ±100.00	
	95% CI	(1 149.15 – 1 279.59)	(848.79 - 976.19)	(656.71 - 723.20)	(620.14 - 718.74)	(557.93 - 754.07)	(249.50 - 446.15)	(304.47 - 568.26)	(90.88 - 409.12)	
	Min.	100.00	200.00	66.67	300.00	120.00	200.00	200.00	200.00	
	Max.	2 400.00	2 400.00	800.00	800.00	800.00	800.00	800.00	400.00	
	Med.	1 000.00	800.00	666.67	666.67	733.33	200.00	400.00	200.00	

Table 3.1 Prescribed daily doses per prescription per year stratified by age groups (continued)

		>12, ≤18 years								
FQ		**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	***p* - value**
Ciprofloxacin	n PDD ± SD 95% CI Min. Max. Med.	4 691 1 319.84 ± 959.03 (1 292.39 – 1 347.29) 25.00 2 500.00 1 000.00	5 071 1 081.04 ± 857.74 (1 057.42 - 1 104.66) 8.33 4 000.00 1 000.00	4 705 954.00 ± 355.30 (943.84 - 964.15) 50.00 1 666.67 1 000.00	3 499 956.70 ± 376.04 (944.23 - 969.17) 16.67 8 333.33 1 000.00	4 005 958.15 ± 345.79 (947.44 - 968.86) 33.33 1 666.67 1 000.00	3 370 930.59 ± 339.88 (919.11 - 942.06) 16.67 1 666.67 1 000.00	2 384 953.08 ± 328.73 (939.88 - 966.28) 16.67 1 666.67 1 000.00	2 097 945.65 ± 331.64 (931.45 - 959.86) 8.33 1 666.67 1 000.00	0.0001
Enoxacin	n PDD ± SD 95% CI Min. Max. Med.	-	1 700.00 ± 0.00 - 700.00 700.00 700.00	-	-	-	-	-	-	-
Gatifloxacin	n PDD ± SD 95% CI Min. Max. Med.	167 425.63 ± 174.69 (398.94 - 452.32) 140.00 1 400.00 400.00	97 444.18 ± 281.06 (387.54 - 500.83) 285.71 2 800.00 400.00	9 400.00 ± 0.00 - 400.00 400.00 400.00	1 400.00 ± 0.00 - 400.00 400.00 400.00	-	-	-	-	0.88
Gemifloxacin	n PDD ± SD 95% CI Min. Max. Med.	217 367.41 ± 167.84 (344.95 - 389.86) 74.67 1 120.00 320.00	247 368.83 ± 262.10 (335.98 - 401.68) 53.33 533.33 320.00	292 314.56 ± 41.53 (309.77 - 319.34) 53.33 533.33 320.00	186 320.00 ± 0.00 - 320.00 320.00 320.00	189 315.23 ± 33.22 (310.46 - 319.99) 53.33 320.00 320.00	128 316.08 ± 27.08 (311.34 - 320.81) 80.00 320.00 320.00	38 320.00 ± 0.00 - 320.00 320.00 320.00	25 309.33 ± 53.33 (287.32 - 331.35) 53.33 1 000.00 500.00	0.0001
Levofloxacin	n PDD ± SD 95% CI Min. Max. Med.	732 534.48 ± 348.38 (509.20 - 559.75) 41.67 2 500.00 500.00	904 505.21 ± 246.53 (489.12 - 521.30) 41.67 1 000.00 500.00	799 530.83 ± 228.63 (514.96 - 546.71) 41.67 1 000.00 500.00	709 575.49 ± 217.08 (559.48 - 591.49) 83.33 1 000.00 500.00	1 037 611.64 ± 232.21 (597.49 - 625.79) 83.33 1 000.00 500.00	682 593.06 ± 210.01 (577.27 - 608.85) 83.33 1 000.00 500.00	416 594.25 ± 220.31 (573.01 - 615.48) 83.33 1 000.00 500.00	380 595.09 ± 208.72 (574.03 - 616.14) 125.00 1 000.00 500.00	0.0001
Lomefloxacin	n PDD ± SD 95% CI Min. Max. Med.	15 706.67 ± 549.63 (402.29 - 1011.04) 400.00 2 000.00 400.00	32 487.50 ± 143.12 (435.90 - 539.10) 200.00 1 000.00 400.00	6 400.00 ± 0.00 - 400.00 400.00 400.00	6 400.00 ± 0.00 - 400.00 400.00 400.00	6 400.00 ± 0.00 - 400.00 400.00 400.00	1 400.00 ± 0.00 - 400.00 400.00 400.00	-	-	0.09

Table 3.1 Prescribed daily doses per prescription per year stratified by age groups (continued)

		>12, ≤18 years								
FQ		**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	***p* - value**
Moxifloxacin	n	782	989	1 009	715	716	560	375	338	0.0001
	PDD ± SD	581.36 ± 181.97	441.82 ± 229.78	394.10 ± 66.65	396.06 ± 34.50	398.90 ± 27.87	396.44 ± 29.11	396.63 ± 31.54	397.52 ± 23.63	
	95% CI	(454.17 - 708.56)	(427.49 - 456.16)	(389.98 - 398.22)	(393.52 - 398.59)	(396.86 - 400.95)	(394.02 - 398.86)	(393.43 - 399.83)	(394.99 - 400.05)	
	Min.	66.67	66.67	66.67	66.67	68.96	66.67	66.67	133.33	
	Max.	5 000.00	2 000.00	2 000.00	400.00	666.67	400.00	400.00	400.00	
	Med.	400.00	400.00	400.00	400.00	400.00	400.00	400.00	400.00	
Norfloxacin	n	620	556	434	315	292	199	167	111	0.0001
	PDD ± SD	1 143.29 ± 668.92	987.19 ± 529.29	773.46 ± 106.70	783.40 ± 82.43	772.16 ± 106.43	764.23 ± 124.44	750.20 ± 139.97	779.10 ± 88.11	
	95% CI	(1 090.53 – 1 196.05)	(943.10 - 1031.29)	(763.39 - 783.52)	(774.26 - 792.54)	(759.90 - 784.42)	(746.84 - 781.63)	(728.81 - 771.58)	(762.53 - 795.67)	
	Min.	40.00	57.14	80.00	165.63	80.00	80.00	82.76	400.00	
	Max.	6 000.00	6 000.00	800.00	800.00	800.00	800.00	800.00	800.00	
	Med.	1 200.00	800.00	800.00	800.00	800.00	800.00	800.00	400.00	
Ofloxacin	n	761	630	373	262	170	109	36	33	0.0001
	PDD ± SD	1 195.69 ± 549.88	958.23 ± 478.81	717.29 ± 135.46	685.98 ± 158.52	711.18 ± 152.60	599.74 ± 241.56	671.30 ± 223.70	647.47 ± 206.67	
	95% CI	(1 156.56 – 1 234.82)	(920.77 - 995.69)	(703.50 - 731.08)	(666.69 - 705.26)	(688.07 - 734.28)	(553.88 - 645.60)	(595.61 - 746.99)	(574.19 - 720.75)	
	Min.	66.67	66.67	200.00	100.00	200.00	171.43	200.00	200.00	
	Max.	4 000.00	4 500.00	800.00	800.00	800.00	800.00	800.00	800.00	
	Med.	1 000.00	800.00	800.00	800.00	800.00	800.00	800.00	800.00	

Where FQ – Fluoroquinolone; n – number of fluoroquinolone agents; PDD – prescribed daily dose (average); SD – standard deviation; CI – confidence interval ; Min. – minimum prescribed dose; Max. – maximum prescribed dose; and Med. - median

Table 3.2 Prescribed daily doses per prescription per year of fluoroquinolones in patients 18 years and younger stratified by prescribers' speciality

Year		General medical practice	Paediatrician	Pharmacotherapist	Specialist	Other	*p* - value
		Ciprofloxacin					
2005	n	5 483	119	4	74	190	< 0.0001
	PDD ± SD	1 334.43 ± 1 103.74	657.34 ± 314.91	750.00 ± 288.68	820.95 ± 450.49	743.53 ± 432.09	
	95% CI	(1 305.21 – 1 363.65)	(600.17 - 714.50)	(290.65 - 1209.35)	(716.57 - 925.32)	(681.70 - 805.37)	
	Min.	50.00	50.00	250.00	250.00	50.00	
	Max.	5 000.00	2 500.00	1 000.00	3 750.00	3 750.00	
	Med.	1 000.00	500.00	750.00	1 000.00	500.00	
2006	n	5 906	164	3	60	200	< 0.0001
	PDD ± SD	1 088.65 ± 845.01	658.42 ± 286.27	666.67 ± 288.68	709.72 ± 302.41	733.37 ± 280.68	
	95% CI	(1 067.10 – 1 110.21)	(614.28 - 702.56)	(-50.44 - 1383.78)	(631.60 - 787.84)	(694.23 - 772.51)	
	Min.	50.00	50.00	250.00	50.00	50.00	
	Max.	5 000.00	1 500.00	1 000.00	1 500.00	1 500.00	
	Med.	1 000.00	500.00	500.00	500.00	500.00	
2007	n	5433	173	1	58	174	< 0.0001
	PDD ± SD	943.98 ± 370.03	737.03 ± 349.05	500.00 ± 0.00	802.75 ± 245.21	726.38 ± 282.98	
	95% CI	(934.13 - 953.82)	(684.65 - 789.41)	-	(738.28 - 867.22)	(684.04 - 768.72)	
	Min.	50.00	50.00	500.00	50.00	50.00	
	Max.	1 666.67	2 500.00	500.00	1 071.43	1 666.67	
	Med.	1 000.00	714.28	500.00	1 000.00	500.00	
2008	n	3893	133	1	52	153	< 0.0001
	PDD ± SD	956.85 ± 383.97	753.46 ± 287.31	1000.00 ± 0.00	682.05 ± 287.73	796.02 ± 276.65	
	95% CI	(944.78 - 968.91)	(704.18 - 802.74)	-	(601.95 - 762.16)	(751.83 - 840.20)	
	Min.	50.00	50.00	500.00	250.00	50.00	
	Max.	8 333.33	1 666.67	1 000.00	1 000.00	1 500.00	
	Med.	1 000.00	714.29	1 000.00	500.00	500.00	
2009	n	4516	242		58	194	< 0.0001
	PDD ± SD	982.78 ± 1229.70	713.25 ± 323.80		759.85 ± 282.07	760.51 ± 284.03	
	95% CI	(946.90 – 1 018.65)	(672.25 - 754.25)	-	(685.69 - 834.02)	(720.29 - 800.73)	
	Min.	50.00	50.00		50.00	50.00	
	Max.	2 500.00	2 500.00		1 500.00	1 666.67	
	Med.	1 000.00	500.00		1 000.00	1 000.00	

Table 3.2 Prescribed daily doses per prescription per year of fluoroquinolones in patients 18 years and younger stratified by prescribers' speciality (continued)

Year		General medical practice	Paediatrician	Pharmacotherapist	Specialist	Other	*p* - value
		Ciprofloxacin					
2010	n	3747	224		56	155	< 0.0001
	PDD ± SD	926.48 ± 351.79	806.22 ± 510.31		739.58 ± 264.39	785.07 ± 267.38	
	95% CI	(915.22 - 937.75)	(739.03 - 873.41)	-	(668.78 - 810.39)	(742.64 - 827.50)	
	Min.	50.00	50.00		50.00	50.00	
	Max.	2 000.00	5 000.00		1 000.00	1 500.00	
	Med.	1 000.00	833.33		770.83	1 000.00	
2011	n	2712	150		37	106	< 0.0001
	PDD ± SD	943.19 ± 346.84	746.75 ± 297.84		787.26 ± 312.41	901.35 ± 329.12	
	95% CI	(930.13 - 956.25)	(698.69 - 794.80)		(683.09 - 891.42)	(837.96 - 964.73)	
	Min.	50.00	50.00	-	50.00	50.00	
	Max.	3 333.33	1666.67		1 500.00	2 500.00	
	Med.	1 000.00	714.28		1 000.00	1 000.00	
2012	n	2443	147		27	102	< 0.0001
	PDD ± SD	940.79 ± 340.61	766.32 ± 291.56		865.96 ± 256.28	740.94 ± 269.91	
	95% CI	(927.27 - 954.30)	(718.79 - 813.84)		(764.58 - 967.34)	(687.93 - 793.96)	
	Min.	50.00	50.00	-	50.00	50.00	
	Max.	1 875.00	1666.67		1 500.00	1 000.00	
	Med.	1 000.00	714.28		1 000.00	833.33	
		Moxifloxacin					
2005	n	822	11	1	10	50	0.93
	PDD ± SD	583.51 ± 176.99	400.00 ± 0.00	400.00 ± 0.00	400.00 ± 0.00	385.33 ± 59.16	
	95% CI	(462.40 - 704.62)	-	-	-	(368.52 - 402.15)	
	Min.	400.00	400.00	400.00	400.00	400.00	
	Max.	2 000.00	400.00	400.00	400.00	400.00	
	Med.	400.00	400.00	400.00	400.00	400.00	
2006	n	1 005	17		15	76	0.09
	PDD ± SD	448.36 ± 256.60	400.00 ± 0.00		377.78 ± 86.07	384.56 ± 66.26	
	95% CI	(432.48 - 464.25)	-	-	(330.12 - 425.44)	(369.42 - 399.70)	
	Min.	400.00	400.00		400.00	400.00	
	Max.	400.00	400.00		400.00	400.00	
	Med.	400.00	400.00		400.00	400.00	

Table 3.2 Prescribed daily doses per prescription per year of fluoroquinolones in patients 18 years and younger stratified by prescribers' speciality (continued)

Year		General medical practice	Paediatrician	Pharmacotherapist	Specialist	Other	*p* - value
		Moxifloxacin					
2007	n	1 025	6		18	66	0.73
	PDD ± SD	(393.58 ± 66.85)	400.00 ± 0.00		381.48 ± 78.57	400.00 ± 0.00	
	95% CI	2 000.00	-	-	(342.41 - 420.55)	(389.48 - 397.67)	
	Min.	400.00	400.00		400.00	400.00	
	Max.	400.00	400.00		400.00	400.00	
	Med.	400.00	400.00		400.00	400.00	
2008	n	704	8		10	52	0.82
	PDD ± SD	396.00 ± 34.77	400.00 ± 0.00		400.00 ± 0.00	400.00 ± 0.00	
	95% CI	(393.42 - 398.57)	-	-	-	-	
	Min.	400.00	400.00		400.00	400.00	
	Max.	400.00	400.00		400.00	400.00	
	Med.	400.00	400.00		400.00	400.00	
2009	n	707	17		7	66	0.40
	PDD ± SD	398.60 ± 30.17	400.00 ± 0.00		382.86 ± 45.36	394.55 ± 31.29	
	95% CI	(396.38 - 400.83)	-	-	(340.91 - 424.80)	(386.85 - 402.24)	
	Min.	400.00	400.00		400.00	400.00	
	Max.	400.00	400.00		400.00	400.00	
	Med.	400.00	400.00		400.00	400.00	
2010	n	535	10		17	59	0.85
	PDD ± SD	395.03 ± 34.04	400.00 ± 0.00		400.00 ± 0.00	397.29 ± 20.83	
	95% CI	(392.14 - 397.92)	-	-	-	(391.86 - 402.72)	
	Min.	400.00	400.00		400.00	400.00	
	Max.	400.00	400.00		400.00	400.00	
	Med.	400.00	400.00		400.00	400.00	
2011	n	364	7		5	39	0.88
	PDD ± SD	396.21 ± 32.53	400.00 ± 0.00		400.00 ± 0.00	400.00 ± 0.00	
	95% CI	392.86	-	-	-	-	
	Min.	400.00	400.00		400.00	400.00	
	Max.	400.00	400.00		400.00	400.00	
	Med.	400.00	400.00		400.00	400.00	
2012	n	341	2		3	27	0.95
	PDD ± SD	397.54 ± 23.53	400.00 ± 0.00		400.00 ± 0.00	400.00 ± 0.00	
	95% CI	(395.04 - 400.05)	-	-	-	-	
	Min.	400.00	400.00		400.00	400.00	
	Max.	400.00	400.00		400.00	400.00	
	Med.	400.00	400.00		400.00	400.00	

Table 3.2 Prescribed daily doses per prescription per year of fluoroquinolones in patients 18 years and younger stratified by prescribers' speciality (continued)

Year		General medical practice	Paediatrician	Pharmaccotherapist	Specialist	Other	*p* – value
		Levofloxacin					
2005	n	757	30	1	19	46	0.53
	PDD ± SD	544.47 ± 385.52	488.89 ± 202.63	250.00 ± 0.00	434.21 ± 183.37	508.39 ± 198.36	
	95% CI	(516.97 - 571.98)	(413.22 - 564.55)	-	(345.83 - 522.59)	(449.48 - 567.29)	
	Min.	250.00	250.00	500.00	250.00	250.00	
	Max.	2 500.00	500.00	500.00	1 000.00	1 000.00	
	Med.	500.00	500.00	500.00	500.00	500.00	
2006	n	948	18	1	26	57	0.95
	PDD ± SD	499.02 ± 243.54	541.67 ± 176.78	500.00 ± 0.00	518.03 ± 233.88	504.39 ± 197.59	
	95% CI	(483.50 - 514.55)	(453.76 - 629.58)	-	(423.56 - 612.50)	(451.96 - 556.81)	
	Min.	250.00	250.00	500.00	250.00	250.00	
	Max.	2 500.00	500.00	500.00	1 000.00	1 000.00	
	Med.	500.00	500.00	500.00	500.00	500.00	
2007	n	803	20		23	55	0.69
	PDD ± SD	530.99 ± 232.13	543.75 ± 237.82		510.87 ± 219.48	495.45 ± 189.36	
	95% CI	(514.91 - 547.07)	(432.45 - 655.05)	-	(415.96 - 605.78)	(444.26 - 546.65)	
	Min.	250.00	250.00		250.00	250.00	
	Max.	1 000.00	1 000.00		1 000.00	1 000.00	
	Med.	500.00	500.00		500.00	500.00	
2008	n	729	13		12	44	0.09
	PDD ± SD	573.56 ± 215.39	660.26 ± 264.53		666.67 ± 325.67	523.13 ± 219.67	
	95% CI	(557.90 - 589.22)	(500.40 - 820.11)	-	(459.75 - 873.59)	(456.35 - 589.92)	
	Min.	250.00	250.00		250.00	250.00	
	Max.	1 000.00	1 000.00		1 050.00	1 000.00	
	Med.	500.00	500.00		625.00	500.00	
2009	n	1057	15		31	60	0.21
	PDD ± SD	606.52 ± 233.34	486.11 ± 229.12		581.22 ± 251.86	620.44 ± 236.71	
	95% CI	(592.44 - 620.60)	(359.23 - 612.99)	-	(488.84 - 673.60)	(559.29 - 681.59)	
	Min.	250.00	250.00		250.00	250.00	
	Max.	1 000.00	1 000.00		1 000.00	1 000.00	
	Med.	500.00	500.00		500.00	500.00	
2010	n	660	11		21	66	0.27
	PDD ± SD	584.57 ± 214.09	481.82 ± 252.26		592.86 ± 254.60	549.24 ± 220.23	
	95% CI	(568.21 - 600.94)	(312.35 - 651.29)	-	(476.96 - 708.75)	(495.10 - 603.38)	
	Min.	250.00	250.00		250.00	250.00	
	Max.	1 000.00	1 000.00		1 000.00	1 000.00	
	Med.	500.00	500.00		500.00	500.00	

Table 3.2 Prescribed daily doses per prescription per year of fluoroquinolones in patients 18 years and younger stratified by prescribers' speciality (continued)

Year		General medical practice	Paediatrician	Pharmacotherapist	Specialist	Other	*p* – value
		Levofloxacin					
2011	n	419	6		10	31	0.27
	PDD ± SD	581.12 ± 217.38	652.78 ± 385.2		455.00 ± 151.75	592.74 ± 245.73	
	95% CI	560.25	248.53	-	346.45	502.61	
	Min.	250.00	250.00		250.00	250.00	
	Max.	1 000.00	1000.00		725.00	1 000.00	
	Med.	500.00	708.33		500.00	500.00	
2012	n	384	8		8	27	0.26
	PDD ± SD	580.53 ± 213.43	625.00 ± 231.46		437.50 ± 115.73	592.59 ± 220.88	
	95% CI	(559.12 - 601.95)	(431.50 - 818.50)	-	(340.75 - 534.25)	(505.21 - 679.97)	
	Min.	250.00	250.00		250.00	250.00	
	Max.	1 000.00	1 000.00		500.00	1 000.00	
	Med.	500.00	500.00		500.00	500.00	
		Ofloxacin					
2005	n	979	2	1		14	0.0001
	PDD ± SD	1 212.82 ± 534.31	586.67 ± 301.70	400.00 ± 0.00		465.31 ± 196.49	
	95% CI	(1 179.31 – 1 246.33)	(2 123.99 – 3 297.32)	-	-	(351.85 - 578.76)	
	Min.	200.00	200.00	400.00		200.00	
	Max.	4 000.00	800.00	400.00		800.00	
	Med.	1 000.00	586.67	400.00		400.00	
2006	n	756	4		3	7	0.012
	PDD ± SD	956.23 ± 461.90	600.00 ± 230.94		577.78 ± 384.90	506.12 ± 201.84	
	95% CI	(923.25 - 989.20)	(232.52 - 967.48)	-	(378.37 – 1 533.92)	(319.45 - 692.79)	
	Min.	200.00	200.00		200.00	400.00	
	Max.	4 000.00	800.00		800.00	800.00	
	Med.	800.00	600.00		800.00	800.00	
2007	n	437			2	9	0.008
	PDD ± SD	715.10 ± 134.44			800.00 ± 0.00	577.78 ± 210.82	
	95% CI	(702.46 - 727.74)	-	-	-	(415.73 - 739.83)	
	Min.	200.00			400.00	400.00	
	Max.	800.00			400.00	800.00	
	Med.	800.00			400.00	800.00	
2008	n	293			1	5	0.17
	PDD ± SD	684.73 ± 156.02			400.00 ± 0.00	720.00 ± 178.89	
	95% CI	(666.79 - 702.67)	-	-	-	(497.88 - 942.12)	
	Min.	200.00			400.00	400.00	
	Max.	800.00			800.00	800.00	
	Med.	800.00			800.00	800.00	

Table 3.2 Prescribed daily doses per prescription per year of fluoroquinolones in patients 18 years and younger stratified by prescribers' speciality (continued)

Year		General medical practice	Paediatrician	Pharmacotherapist	Specialist	Other	*p* – value
		Ofloxacin					
2009	n	180	5		1	4	< 0.0001
	PDD ± SD	715.00 ± 148.79	344.00 ± 125.22		800.00 ± 0.00	700.00 ± 200.00	
	95% CI	(693.12 - 736.88)	(188.52 - 499.48)	-	-	(381.76 - 1018.24)	
	Min.	200.00	200.00		400.00	200.00	
	Max.	800.00	400.00		800.00	800.00	
	Med.	800.00	400.00		800.00	800.00	
2010	n	121	9			2	< 0.0001
	PDD ± SD	581.58 ± 247.34	200.00 ± 0.00			600.00 ± 282.84	
	95% CI	(537.06 - 626.10)	-	-	-	(-1 941.24 – 3 141.24)	
	Min.	200.00	200.00			400.00	
	Max.	800.00	200.00			800.00	
	Med.	666.67	200.00			600.00	
2011	n	46				1	0.36
	PDD ± SD	621.01 ± 238.24				400.00 ± 0.00	
	95% CI	(550.27 - 691.76)	-	-	-	-	
	Min.	200.00				200.00	
	Max.	800.00				400.00	
	Med.	800.00				400.00	
2012	n	39				1	0.41
	PDD ± SD	599.15 ± 238.48				800.00 ± 0.00	
	95% CI	(521.84 - 676.45)	-	-	-	-	
	Min.	200.00				400.00	
	Max.	800.00				800.00	
	Med.	666.67				800.00	
		Enoxacin					
2006	n	2					-
	PDD ± SD	550.00 ± 212.13					
	95% CI	(-1 355.93 – 2 455.93)	-	-	-	-	
	Min.	200.00					
	Max.	700.00					
	Med.	550.00					

Table 3.2 Prescribed daily doses per prescription per year of fluoroquinolones in patients 18 years and younger stratified by prescribers' speciality (continued)

Year		General medical practice	Paediatrician	Pharmacotherapist	Specialist	Other	*p* – value
		Gatifloxacin					
2005	n	159	15	1		28	0.28
	PDD ± SD	434.47 ± 194.00	320.00 ± 101.42	400.00 ± 0.00		428.57 ± 194.09	
	95% CI	(404.08 - 464.85)	(263.84 -376.16)	-	-	(353.31 - 503.83)	
	Min.	400.00	400.00	400.00		1 400.00	
	Max.	1 400.00	400.00	400.00		400.00	
	Med.	1 000.00	400.00	400.00		400.00	
2006	n	92	9	265		28	0.63
	PDD ± SD	446.58 ± 288.49	364.44 ±73.33	369.82 ± 260.79		428.57 ± 194.09	
	95% CI	(386.84 - 506.33)	(308.08 - 420.81)	(338.28 - 401.36)	-	(353.31 - 503.83)	
	Min.	400.00	400.00	400.00		400.00	
	Max.	2 800.00	400.00	400.00		1 400.00	
	Med.	400.00	400.00	400.00		400.00	
2007	n	10	2				-
	PDD ± SD	400.00 ± 0.00	400.00 ± 0.00				
	95% CI	-	-	-	-	-	
	Min.	400.00	400.00				
	Max.	400.00	400.00				
	Med.	400.00	400.00				
2008	n	1	8				-
	PDD ± SD	400.00 ± 0.00	400.00 ± 0.00				
	95% CI	-	-	-	-	-	
	Min.	400.00	400.00				
	Max.	400.00	400.00				
	Med.	400.00	400.00				
		Norfloxacin					
2005	n	701	2	1		10	0.21
	PDD ± SD	1 126.92 ± 640.49	800.00 ± 0.00	800.00 ± 0.00		732.00 ± 215.03	
	95% CI	(1 079.43 – 1 174.42)	-	-	-	(578.17 - 885.83)	
	Min.	400.00	400.00	400.00		400.00	
	Max.	6 000.00	800.00	800.00		800.00	
	Med.	1 200.00	800.00	800.00		800.00	
2006	n	626	1		2	10	0.53
	PDD ± SD	979.62 ± 510.71	800.00 ± 0.00		800.00 ± 0.00	760.00 ± 126.49	
	95% CI	(939.53 – 1 019.70)	-	-	-	(669.51 - 850.49)	
	Min.	400.00	400.00		400.00	400.00	
	Max.	6 000.00	800.00		800.00	800.00	
	Med.	800.00	800.00		800.00	800.00	

Table 3.2 Prescribed daily doses per prescription per year of fluoroquinolones in patients 18 years and younger stratified by prescribers' speciality (continued)

Year		General medical practice	Paediatrician	Pharmacotherapist	Specialist	Other	*p* - value
		Norfloxacin					
2007	n	475	1		5	8	< 0.0001
	PDD ± SD	777.77 ± 103.23	400.00 ± 0.00		600.00 ± 282.84	710.00 ± 168.01	
	95% CI	(768.46 - 787.08)	-	-	(248.80 - 951.20)	(569.54 - 850.46)	
	Min.	400.00	400.00		400.00	400.00	
	Max.	4 200.00	800.00		800.00	800.00	
	Med.	800.00	800.00		800.00	800.00	
2008	n	363	1		2	4	0.35
	PDD ± SD	780.86 ± 89.04	800.00 ± 0.00		800.00 ± 0.00	700.00 ± 200.00	
	95% CI	(771.67 - 790.05)	-	-	-	(381.76 – 1 018.24)	
	Min.	400.00	400.00		400.00	400.00	
	Max.	800.00	800.00		800.00	800.00	
	Med.	800.00	800.00		800.00	800.00	
2009	n	315			180	7	0.74
	PDD ± SD	771.40 ± 108.27			338.89	742.86 ± 151.19	
	95% CI	(759.39 - 783.40)	-	-	325.30	(603.03 - 882.68)	
	Min.	400.00			400.00	400.00	
	Max.	800.00			800.00	800.00	
	Med.	800.00			800.00	800.00	
2010	n	223	2			2	0.82
	PDD ± SD	755.89 ± 137.37	800.00 ± 0.00			800.00 ± 0.00	
	95% CI	(737.76 - 774.02)	-	-	-	-	
	Min.	400.00	400.00			400.00	
	Max.	800.00	800.00			800.00	
	Med.	800.00	800.00			800.00	
2011	n	173			5	4	0.03
	PDD ± SD	744.29 ± 147.70			800.00 ± 0.00	620.00 ± 210.40	
	95% CI	(722.13 - 766.46)	-	-	-	(285.21 - 954.79)	
	Min.	400.00			400.00	400.00	
	Max.	800.00			400.00	800.00	
	Med.	800.00			400.00	640.00	
2012	n	122				4	0.63
	PDD ± SD	777.70 ± 90.99				800.00 ± 0.00	
	95% CI	(761.40 - 794.01)	-	-	-	-	
	Min.	400.00				400.00	
	Max.	800.00				800.00	
	Med.	800.00				800.00	

Table 3.2 Prescribed daily doses per prescription per year of fluoroquinolones in patients 18 years and younger stratified by prescribers' speciality (continued)

Year		General medical practice	Paediatrician	Pharmacotherapist	Specialist	Other	*p* - value
		Gemifloxacin					
2005	n	231			2	12	0.52
	PDD ± SD	373.77 ± 176.04			320.00 ± 0.00	320.00 ± 0.00	
	95% CI	(350.95 - 396.59)	-	-	-	-	
	Min.	320.00			320.00	320.00	
	Max.	1 120.00			320.00	320.00	
	Med.	320			320.00	320.00	
2006	n	265	3		1	18	0.85
	PDD ± SD	266.67 ± 92.38	320.00 ± 0.00		320.00 ± 0.00	320.00 ± 0.00	
	95% CI	(37.19 - 496.14)	-	-	-	-	
	Min.	320.00	320.00		320.00	320.00	
	Max.	3 413.00	320.00		320.00	320.00	
	Med.	320.00	320.00		320.00	320.00	
2007	n	320	1		2	11	0.0004
	PDD ± SD	314.37 ± 41.37	320.00 ± 0.00		186.67 ± 188.56	320.00 ± 0.00	
	95% CI	(309.82 - 318.92)	-	-	(-1 507.49 – 1 880.83)	-	
	Min.	320.00	320.00		320.00	320.00	
	Max.	533.33	320.00		320.00	320.00	
	Med.	320	320.00		186.67	320.00	
2008	n	202	1		1	3	-
	PDD ± SD	320.00 ± 0.00	320.00 ± 0.00		320.00 ± 0.00	320.00 ± 0.00	
	95% CI	-	-	-	-	-	
	Min.	320.00	320.00		320.00	320.00	
	Max.	320.00	320.00		320.00	320.00	
	Med.	320.00	320.00		320.00	320.00	
2009	n	197	1		2	6	0.98
	PDD ± SD	315.42 ± 32.55	320.00 ± 0.00		320.00 ± 0.00	320.00 ± 0.00	
	95% CI	(310.85 - 319.99)	-	-	-	-	
	Min.		320.00		320.00	320.00	
	Max.		320.00		320.00	320.00	
	Med.		320.00		320.00	320.00	
2010	n	129				4	0.77
	PDD ± SD	316.11 ± 26.97				320.00 ± 0.00	
	95% CI	(311.41 - 320.81)	-	-	-	-	
	Min.	320.00				320.00	
	Max.	320.00				320.00	
	Med.					320.00	

Table 3.2 Prescribed daily doses per prescription per year of fluoroquinolones in patients 18 years and younger stratified by prescribers' speciality (continued)

Year		General medical practice	Paediatrician	Pharmacotherapist	Specialist	Other	*p* - value
		Gemifloxacin					
2011	n PDD ± SD 95% CI Min. Max. Med.	41 320.00 ± 0.00 - 320.00 320.00 320.00	1 320.00 ± 0.00 - 320.00 320.00 320.00	-	-	-	-
2012	n PDD ± SD 95% CI Min. Max. Med.	27 310.12 ± 51.32 (289.82 - 330.42) 320.00 320.00 320.00	-	-	-	3 320.00 ± 0.00 - 320.00 320.00 320.00	0.75
	Lomefloxacin						
2005	n PDD ± SD 95% CI Min. Max. Med.	20 760.00 ± 578.93 (489.05 - 1030.95) 400.00 2 000.00 400.00	-	-	-	-	-
2006	n PDD ± SD 95% CI Min. Max. Med.	37 551.35 ± 303.33 (450.21 - 652.49) 400.00 2 000.00 400.00	-	-	-	-	-
2007	n PDD ± SD 95% CI Min. Max. Med.	6 400.00 ± 0.00 - 400.00 400.00 400.00	-	-	-	-	-
2008	n PDD ± SD 95% CI Min. Max. Med.	6 400.00 ± 0.00 - 400.00 400.00 400.00	-	-	-	-	-

Table 3.2 Prescribed daily doses per prescription per year of fluoroquinolones in patients 18 years and younger stratified by prescribers' speciality (continued)

Year		General medical practice	Paediatrician	Pharmacotherapist	Specialist	Other	*p* - value
		Lomefloxacin					
2009	n PDD ± SD 95% CI Min. Max. Med.	6 400.00 ± 0.00 - 400.00 400.00 400.00	-	-	-	-	-
2010	n PDD ± SD 95% CI Min. Max. Med.	1 400.00 ± 0.00 - 400.00 400.00 400.00	-	-	-	-	-

Where n – number of fluoroquinolone agents; PDD – prescribed daily dose (average); SD – standard deviation; CI – confidence interval; Min. – minimum prescribed dose; Max. – maximum prescribed dose; and Med. - median

3.6 Chapter summary

In this chapter, three manuscripts were presented addressing the objectives of the empirical investigation. The chapter concluded with additional results obtained from the empirical investigation. The next chapter, which concludes the study, focuses on the conclusion, strengths and limitations of the study, and recommendations for future studies.

CHAPTER 4: CONCLUSIONS, LIMITATIONS, STRENGTHS AND RECOMMENDATIONS

4.1 Introduction

The focus of the final chapter is to draw conclusions from the study with regard to the specific objectives outlined. This chapter begins with a brief overview of the content of the dissertation and a summary of findings from the study. The strengths and limitations will be outlined, concluding the chapter with recommendations for future studies.

4.2 Content of dissertation

This dissertation consisted of four chapters. Chapter 1 provided a general overview of the study, centring on providing a background, defining the problem, research questions that will be answered, the aim, specific objectives and methodology utilised in the study.

Chapter 2 focused on providing a general summary of antibiotics and their use from literature. The fluoroquinolones as a pharmacological group of antibiotics were extensively discussed in adults and in children 18 years and younger. This was followed by a conceptualisation of antimicrobial resistance and the resistance patterns of clinically relevant bacteria in sub-Saharan Africa. The global usage patterns of antibiotics, with an emphasis on fluoroquinolones, were further investigated. The use of antibiotics was found to have a significant correlation with the emergence of antibiotic resistance, and interventions set up to monitor and control the use of antibiotics globally were identified. The chapter concluded with the quantitative measurement of antibiotic use in health settings with an emphasis on the ATC/DDD methodology.

Chapter 3, representing the results and discussions section of the dissertation, was presented in the form of manuscripts. Additional results were presented in section 3.4. Three manuscripts were presented with the following titles:

- Manuscript 1: Antibiotic prescribing patterns in the South African private health sector (2005-2012).
- Manuscript 2: Fluoroquinolone utilisation patterns in adults in the private health sector of South Africa (2005-2012).
- Manuscript 3: Prescribing patterns of fluoroquinolones in children and adolescents in the private health sector of South Africa (2005-2012).

4.3 Conclusions from the study

The goal of the study was to determine the prescribing patterns of antibiotics with an emphasis on fluoroquinolones in the private health sector in South Africa, analysing eight years' medicine claims data. The study was based on two main approaches focusing on the literature review and the empirical investigation. The empirical study followed a quantitative, descriptive, observational design using retrospective, longitudinal medicine claims data provided by a nationally representative Pharmaceutical Benefit Management company (PBM). The conclusions from the specific research objectives follow in the subsequent paragraphs.

4.3.1 Conclusions from the literature review

The objectives of the literature review outlined in paragraph 1.5, Chapter 1, were achieved in Chapter 2 of this dissertation. The following paragraphs summarise the findings:

- **To conceptualise antibiotics and their use**

Antimicrobials were defined as low molecular microbial metabolites that limit the growth of micro-organisms at low concentrations (Gelone & O'Donnell, 2005:1633; Lancini *et al*., 1995:1). The term has also been referred to semi-synthetic antimicrobials (Chambers, 2001a:1143). In this study, the following pharmacological group of antibiotics were considered: penicillins, cephalosporins, carbapenems, aminoglycosides, chloramphenicol, fluoroquinolone, macrolides, tetracycline, sulphonamides and trimethoprim. The mechanisms of action of penicillins, cephalosporins, carbapenems, aminoglycosides, chloramphenicol, macrolides, tetracycline, sulphonamides and trimethoprim were briefly investigated. The spectrum of activity, adverse effects and clinical uses were summarised briefly (refer to paragraphs 2.2.2.1 to 2.2.2.11).

- **Determine, from literature, fluoroquinolones as a pharmacological group of antibiotics, their indications for use, side effects, drug interactions and special precautions**

Quinolones were extensively covered to achieve the goal of the study. It was established from literature that they are a synthetic group of antibiotics originating from nalidixic acid (Norris & Mandell, 1988:2). The fluorine at position six creates the fluoroquinolone group,

increasing their potency against aerobes (Domagala, 1994:686; Stahlmann & Lode, 1999:305; Wolfson & Hooper, 1985:581). The fluoroquinolones were found to be a very important pharmacological group of antibiotics due to their anti-pseudomonal activity, especially ciprofloxacin (Domagala, 1994:685). As discussed in paragraph 2.2.2.12.2, the fluoroquinolones selectively interact with two bacterial targets, the related enzymes DNA gyrase (topo-isomerase II), an essential bacterial enzyme that keeps the super-helical twists in DNA and that are involved in DNA replication, and topo-isomerase IV, which act in terminal stages of the separation of the interlinked daughter chromosomes (Wolfson & Hooper, 1985:581).

Currently, five distinct generations have been proposed based on their spectrum of activity, *in vitro* properties and clinical uses. The first four major classifications systems have been proposed by Andriole and Schellhorn (1997:64); Ball (2000:18); King *et al.* (2000); and Naber and Adam (1998:255). Andriole and Schellhorn (1997:64); and Ball (2000:18) grouped fluoroquinolones into three main generations, whereas King *et al.* (2000); and Naber and Adam (1998:255) grouped them into four main generations. None of these classifications have been adopted universally, although several sources (Blondeau, 2004:75; Goldman & Kearns, 2011:3; Liu, 2010:355; Oliphant & Green, 2002:457; Scholar, 2002:165; Sharma *et al.,* 2009:588) make reference to King and colleagues' (2000) classification. The latter classification system categorises fluoroquinolones into five main generations (Somasundaram & Manivannan, 2013:298). The fifth group is represented by delafloxacin, which is currently in the development phase (Anon., 2014).

From literature, it was established that fluoroquinolones possess good pharmacokinetic profiles allowing flexible dosing. They were found to have rapid absorption after oral and parenteral administration with peak plasma concentrations being reached one to three hours after administration (Scholar, 2003:166; Sharma *et al*., 2009:597). Their long elimination half-lives permit a once or twice daily dosing regimen (Stein, 1996:19) and their bioavailability is not affected by the presence of food (Oliphant & Green, 2002:455; Sharma *et al*., 2009:597). Fluoroquinolones undergo renal or hepatic clearance, or both (Hooper & Wolfson, 1991:386-387; Oliphant & Green, 2002:455; Scholar, 2003:167).

Due to their broad antimicrobial spectrum, fluoroquinolones are agents of choice for the treatment of uncomplicated and complicated urinary tract infections, acute sinusitis, acute exacerbations of chronic bronchitis, community acquired pneumonia (CAP), skin and skin structure infections, and intra-abdominal infections caused by susceptible organisms (King *et*

al., 2000; McEvoy *et al*., 2002:764-822).

The major side effects of fluoroquinolones were found to be dependent on the structural configuration of the fluoroquinolone compound. The major side effects included gastro-intestinal effects involving nausea (Lober *et al*., 1999:1069), vomiting, dyspepsia and abdominal pain (Stass & Kubitza, 1999:85); central nervous system (CNS) effects involving headache (Stass & Kubitza, 1999:85), dizziness, tiredness and sleepiness (Saravolatz & Legget, 2003:1213); hypersensitivity reactions involving erythema, pruritus, urticaria and rash; photosensitivity reactions, arthralgia; tendonitis (Meyers *et al*., 2013:229); prolongation of the QT interval resulting in arrhythmias and *torsades de pointes* (Lapi *et al.,* 2012:1460); and peripheral neuropathy (Cohen, 2001:1541-1543)

From literature, fluoroquinolones in pre-clinical studies were found to induce changes in the immature articular cartilage of the weight-bearing joints of young laboratory animals (Burkahdt *et al*., 1997:1199; Gough *et al*., 1992:444). Studies have, however, reported few or no incidence of arthralgia and tendonitis in patients (children) 18 years and younger (Arguedas *et al*., 2003; Chalumeau *et al*., 2003; Goldman & Kearns, 2011:2; Hampel *et al*., 1997; Saez-llorenz *et al*., 1997; Yee *et al*., 2002; Zimbabwe *et al.*, 2002). Due to their effectiveness and reported safety (refer to Table 2.9), in 2006, the Committee on Infectious Diseases in the United States (2006:1290) recommended the use of fluoroquinolones in children younger than 18 years in infections caused by MDR pathogens for which there are no safer and effective alternatives. Additionally, they have been indicated when therapies by parenteral route are not possible and there are no other agents available. This recommendation was based on the evaluation of several studies that reported the incidence of mild to moderate incidences of arthralgia.

- **Determine antibiotic prescribing patterns in Europe, United States and Africa with an emphasis on fluoroquinolones; and resistance patterns in Africa**

Antimicrobial resistance was found to be an intrinsic feature in microorganisms whereby the organism has the ability to exchange genetic materials to survive changing environmental conditions and occupy certain ecological niches (Cohen, 1992:1053). The following are resistance mechanisms by microorganisms (Denis *et al.,* 2010:91; Sefton, 2002:560):

- Active expulsion of antibiotic from the bacterial cell by trans-membrane efflux system.
- Modification of the bacterial cell envelope rendering it less permeable to the drug.
- Modification of target site.

- Production of protective proteins at target site.
- Inactivation of the drug by specific enzymes before or after the drug enters the cell of the bacteria.
- Acquisition of target by-pass by a unique metabolic pathway.

Extrinsic factors such as selective pressures influenced by patterns of antimicrobial prescribing and use, societal and technological changes, and poor infection control surveillance systems were also attributed to the emergence of antimicrobial resistance (Essack, 2006:51; Harbath & Samore, 2005:794-795; Laxminarayan *et al.,* 2013).

It was established that globalisation has enabled the rapid spread of infectious disease agents (WHO, 2001:11). Over the years, the incidence and prevalence of resistant strains have been identified globally, and sub-Saharan Africa is no exception (refer to table 2.13). Antimicrobial resistance was found to cause an increase in morbidity, mortality and medical costs associated with infections (Canadian Committee on Antimicrobial Resistance, 2003:159; CDC, 2013:11; Cohen, 1992:1053; Cosgrove *et al*., 2005:171; Crowther-Gibson *et al.*, 2011:567; ECDC, 2009:13; Engemann *et al*., 2003:586; Goossens *et al*., 2007:1093; Laxminarayan *et al.,* 2013; McKenna, 2013; Reed *et al.,* 2005:182). An improvement in the use of antibiotics was found to be an integral part in controlling antimicrobial resistance (WHO, 2001:4-7). In view of this, the global patterns of antibiotics were analysed. From the iconic studies evaluated, the use of antibiotics showed an increase globally (Adriaenssens *et al*., 2011a:6-7; Cars *et al*., 2001:1854; Dumartin *et al*., 2010:2030; Essack *et al.*, 2011:565-566; Ferech *et al*., 2006:403-404; Goossens *et al.*, 2005:381-383; Gould, 2005:122; Janknegt *et al*., 2000:252; Wirtz *et al*., 2010:220). The dominant use of penicillins (especially in combination with a beta-lactamase inhibitor) was observed in most of these studies. Among the fluoroquinolones, ciprofloxacin was the most widely prescribed (Adriaessens *et al.,* 2011b:6-7; Ferech *et al*., 2006:424; Goossens *et al*., 2007:1094; Kotwani & Holloway, 2011:5-6; Polk *et al*., 2004:499; Wirtz *et al*., 2010:220).

- **Identify interventions set up to monitor and control the use of antibiotics globally**

Although the usage of antibiotics was strongly correlated with resistance (Austin *et al.,* 1999:1156; Pechere, 2001:172; Laxminyaran *et al*., 2013), irrational use was found to accelerate resistance to a greater extent (WHO, 2013:25). From the literature, approximately 50% of all hospital visits ended with a prescription for an antibiotic, of which a significant proportion was deemed inappropriate (Abula & Kedir, 2004:37; Al-Ghamdi *et al*., 2002:118;

Gonzales *et al.,* 2001:759; Katende-Kyenda *et al.,* 2006:705; Polk *et al*., 2007:671; Raveh *et al.*, 2001:146; Tunger *et al*., 2000:134). The appropriate use of antibiotics was found to be of prime importance in combating resistance.

Three major groups of interventions for appropriate antibiotic use were identified and are grouped as follows (Davey *et al.,* 2013:6): restrictive, educational and structural interventions. Measuring the outcomes of implemented interventions was found to be expedient in assessing their effectiveness. Among the parameters recommended for assessment, monitoring the changes in total and targeted drug usage before and after implementation were found to be vital (Brown, 2005:180-181).

Units for measuring drug use such as cost figures (Haaijer-Ruskamp & Dukes, 1993:130), prescription volume (WHO, 2003:39) and number of units dispensed (Capella, 1993:59) were identified. These units were found to have major flaws in comparing drug use between countries (MacKenzie & Gould, 2005:105). The ATC/DDD methodology was developed by the WHO to address the shortcomings of the previous units (WHO, 2003:33). The Anatomical Therapeutic Chemical (ATC) classification system categorises drugs into fourteen main groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties; stratified at five different levels (refer to Table 2.14). The first level represents the anatomical group; further narrowing down to the fifth level represented by the chemical substance. Each drug is assigned a distinct ATC code. For example, antibiotics for systemic use, according to the classification, belong to the J01 group at the second level. Fluoroquinolones, a pharmacological group of antibiotics, belong to the J01MA group at the fourth level (refer to Table 2.14).

The defined daily dose (DDD), defined as the assumed average maintenance dose per day for a drug used for its main indication in adults, is a technical unit of measurement developed to quantify drug use devoid of cost and physical units (WHO, 2003:20). DDDs are assigned to drugs at the fifth level of the ATC classification (Hutchinson *et al*., 2004:30). Rates used to express drug use such as DDD per 1 000 inhabitants, DDD per 100 bed-days, and the DDD per inhabitants were identified from literature (WHO, 2013:26). For the purpose of this study, outpatient antibiotic use in adults was quantified using DDD per 1 000 inhabitants (DID).

Quantifying drug use with the DDD, however, does not provide a true reflection of doses prescribed to the patient as it is derived from the average maintenance dose in adults. The prescribed daily dose (PDD) was further identified as an appropriate means of determining

the average dose prescribed according to a representative sample of prescriptions. A major advantage of the PDD over the DDD is its appropriateness in describing drug use, especially in children.

4.3.2 Conclusions from the empirical investigation

The objectives of the empirical investigation were realised in Chapter 3. Three manuscripts were developed from the specific objectives outlined (refer to paragraph 1.4.2). The following paragraphs summarise the findings:

- **Investigating the prescribing patterns of antibiotics *viz*. age, gender, seasonal and geographic variation, over the eight-year period for the various pharmacological groups of antibiotics**

A total of 5 155 262 (44.8%) patients out of the total number of patients who claimed prescriptions received at least one prescription for an antibiotic from 2005 to 2012. Of the total number of prescriptions claimed during the study period, 17.6% represented antibiotic prescriptions and antibiotic agents represented 7.9% of the total number of medicine items claimed. Patients claiming antibiotic prescriptions decreased by 7.9% from 2005 to 2012. The general decrease in antibiotic prescribing may be attributed to antibiotic stewardship programmes initiated in the private health sector in 2009 to promote prudent antibiotic use (Gelband & Duse, 2011:596). From the study, the frequency of antibiotic prescriptions was higher in females (n = 2 831 686, 54.9%) than in males (n = 321 635, 45.1%). The higher proportion of females in the total population of South Africa (Statistics South Africa, 2011) and the pronounced health-seeking behaviour in females (Verbrugge, 1982:430) were provided as possible reasons for the finding. Children and adolescents up to 18 years claimed the most antibiotic prescriptions. The result confirms the high incidence of infections in this age group, since their level of immunity is still under-developed (Katende-kyenda *et al*., 2006:705).

Gauteng had the highest prevalence of patients receiving antibiotics, increasing by 3.3% from 2005 to 2012. This confirmed factors such as high population density, urbanisation, migration and the close proximity in living areas being associated with the increased spread of infections and the use of antibiotics (Alirol *et al*., 2011:133). Conversely, the Northern Cape had the lowest prevalence of patients claiming antibiotics. Patients claiming antibiotic prescriptions in Limpopo, KwaZulu-Natal and the Eastern Cape decreased by 3.1%, 2.7%

and 1.0% respectively during the study period. However, there was no practical association between the prevalence of patients receiving antibiotics and province ($p < 0.0001$, Cramer's $V \leq 0.2$).

Consistent with studies from Europe (Adriaenssens *et al*., 2011a:7) and in South America (Wirtz *et al*., 2010:220), penicillins were the most widely prescribed antibiotic. This was followed by the fluoroquinolones, macrolides and cephalosporins. The carbapenems and chloramphenicol were the least prescribed in all age groups. There was no practical association between the number of antibiotic agents claimed with age, gender or season (Cramer's $V < 0.2$). The use of broad-spectrum antibiotics such as amoxicillin-clavulanic acid, azithromycin, clarithromycin and the sulphadoxine/trimethoprim combination increased more than 0.7% from 2005 to 2012.

Lastly, antibiotic prescribing was found to be high from the months of May to August representing the winter season in South Africa. This confirmed trends in Europe (Adriaenssens *et al*., 2011a:7) and America (Wirtz *et al*., 2010:220). However, no practically significant association was found between antibiotic prescribing and seasonal trends ($p < 0.0001$, Cramer's $V < 0.2$) (refer to manuscript 1).

- **Investigating specifically the prescribing patterns of the various groups of fluoroquinolones focusing on longitudinal prevalence variations using the defined daily dose (DDD) per 1 000 inhabitants per day for adults**

A total of 1 397 960 patients older than 18 years received 1 983 622 fluoroquinolone prescriptions and 1 998 552 fluoroquinolone agents during the study period. Overall, the prevalence of fluoroquinolone prescriptions decreased by 3.6% from 2005 to 2012. Contrary to studies from Europe (Adriaenssens *et al*., 2011b:7), the United States (Linder *et al.*, 2005:263) and eight Latin American countries (Wirtz *et al*., 2010:220) that reported an increase in the use of fluoroquinolones over the past decade, the present study showed a decrease in the number of fluoroquinolone prescriptions claimed from 2005 to 2012.

The average number of fluoroquinolone prescriptions per patient per year ranged from 1.45 ± 0.92 (95% CI 1.44-1.45) in 2005 to 1.31± 0.71 (95% CI 1.31-1.32) in 2012. Females received more fluoroquinolone prescriptions than males did over the study period; 60.8% *vs.* 39.2%. The high prescribing of fluoroquinolones in females may be associated with the increased risk of having urinary tract infection due to the use of spermicides as birth control,

genetic disposition and sexual behaviour (Fihn *et al*., 1996:514; Foxman, 2002:6; Hooton *et al*., 1996:469; Lindsay, 2002:135-136). The highest prevalence of fluoroquinolone prescriptions was observed in the age group 45 to 65 years, representing 37% (n = 511 542) of patients who received a prescription for fluoroquinolone. This finding was in contrast with other studies that observed the highest use in patients above 65 years (Blix *et al*., 2007:973; Franchi *et al*., 2011:304; Gallini *et al*., 2012:2913; Lallana-Alvarez *et al*., 2012:593; Litwin & Saigal, 2012:365; Majeed & Moser, 1999:736). However, no practically significant association was found between the prevalence of fluoroquinolone prescriptions and gender ($p < 0.0001$, Cramer's $V = 0.02$) or age group ($p < 0.0001$, Cramer's $V = 0.04$) during the study period. Additionally, no practically significant differences were found between the average DDD per prescription per patient over the study period (Cohen's d-value < 0.8).

Norfloxacin was the only first-generation fluoroquinolone prescribed. Its use decreased during the study period confirming Adriaenssens *et al.'s* (2011b:6) study involving 33 European countries. The second-generation fluoroquinolones accounted for the majority of all the fluoroquinolone agents prescribed during the study period. Ciprofloxacin was the most prescribed fluoroquinolone, consistent with studies conducted in Europe (Adriaenssens *et al*., 2011b:6), the United States (Goossens *et al*., 2007:1093, Linder *et al*., 2005:262), eight Latin American countries (Wirtz *et al*., 2010:220) and Tanzania (Van de Boogaard *et al.*, 2010:146). The use of ciprofloxacin was, however, found to decrease over the study period. This decrease was attributed to the shift from ciprofloxacin to cefixime in 2008 in the treatment of gonococcal infection due to resistance to ciprofloxacin (Crowther-Gibson *et al*., 2011:574). Levofloxacin was the second most prescribed fluoroquinolone, increasing by 0.21 DID from 2005 to 2012. Moxifloxacin and gatifloxacin were the only third-generation fluoroquinolone prescribed. Moxifloxacin was the most prescribed fluoroquinolone in this generation. Gatifloxacin use was only observed from 2005 to 2008 due to its withdrawal from the market due to safety concerns in 2008 (Baker *et al.,* 2006; FDA, 2008) (refer to manuscript 2).

- **Describing the prescribing patterns of the various groups of fluoroquinolones in children *viz*. age, gender and speciality of prescribers over the study period comparing the prescribed daily dosages (PDD) to the recommended daily doses (RDD)**

A total of 1 366 824 patients, 18 years and younger, claimed antibiotic prescriptions, of which 3.6% (n = 49 540) received at least one prescription for a fluoroquinolone during the

study period. The percentage of patients receiving fluoroquinolone prescriptions decreased by 0.7% from 2005 to 2012. Overall, 57 325 prescriptions for fluoroquinolones and 57 593 fluoroquinolone agents were claimed.

The prevalence of fluoroquinolone prescriptions was higher in females throughout the study period. The highest prevalence of patients receiving fluoroquinolone prescriptions was observed in patients between 12 and 18 years; and the lowest prevalence was observed in patients five years and younger, confirming the trends in France (Genuini *et al*., 2014) and the United States (Committee on Infectious Diseases, 2006:1280). Ciprofloxacin was the most prescribed fluoroquinolone in all the age groups, though its use decreased over the study period. In South Africa, ciprofloxacin is the only fluoroquinolone with several indications in paediatrics such as typhoid fever, shigellosis, cholera and chemoprophylaxis of bacterial meningitis in close contact (Department of Health, 2013). From the literature, although there were outbreaks of typhoid fever in 2005 (Keddy *et al*., 2011:140) and cholera (Blumberg *et al.*, 2011:196) between 2008 and 2009, the incidences of bacterial meningitis, shigellosis and typhoid fever decreased over the study period.

Levofloxacin and moxifloxacin were the second most used fluoroquinolones in all the age groups. They are included together with ofloxacin in the treatment of MDR-TB in children (Department of Health, 2013). MDR-TB cases are mostly treated in the public health sector. Usage in the private sector was not certain as data on diagnoses were incomplete (refer to manuscript 3).

Dosing of fluoroquinolones in children is essential to achieve the desired therapeutic effects and to limit resistance (Alghasham & Nahata, 2000:348). In 2005, maximum doses for ofloxacin and moxifloxacin were exceeded in children five years and younger; and in children between 12 and 18 years, maximum doses were exceeded for ofloxacin, moxifloxacin and norfloxacin in 2005 and 2006. The reason for this observation was, however, not certain.

Practically significant differences were found in the average PPDs between 2005 and the other years under study for norfloxacin in children between five and 12 years (Cohen's *d*-value ≥ 0.84); between 2006 and 2010 (Cohen's *d*-value = 0.83) and between 2006 and 2011 (Cohen's *d*-value = 1.04) in patients between 12 and 18 years. For ofloxacin, practically significant differences were found in the average PPDs between 2005 and the subsequent years in patients between five and 12 years (Cohen's *d*-value ≥ 0.80); between 2006 and 2010, 2011, 2012 (Cohen's *d*-value ≥ 1.43); between 2007 and 2010, 2012

(Cohen's *d*-value ≥ 0.87); between 2008 and 2010, 2012 (Cohen's *d*-value ≥ 0.82); and between 2009 and 2012 (Cohen's *d*-value = 1.03) in patients between five and 12 years, practically significant differences were found in the average PPDs between 2005 and the other years under study (Cohen's *d*-value ≥ 1.16); and between 2006 and 2010 (Cohen's *d*-value = 0.87) (refer to paragraph 3.5.1). Lastly, for norfloxacin, practically significant differences were observed in the differences in the average PPDs between 2005 and the other years under study (Cohen's *d*-value ≥ 0.88).

In all age groups, general medical practitioners accounted for most fluoroquinolone prescribing. They were accountable for high doses prescribed for all fluoroquinolones dispensed (refer to paragraph 3.4). In 2007, general medical practitioners prescribed higher doses of ciprofloxacin than pharmacotherapists did (Cohen's *d*-value = 1.24). PDDs for ofloxacin were observed to be higher in general medical practitioners than the rest of the prescribers in 2005 (Cohen's *d*-value ≥ 1.41) and in 2006 (Cohen's *d*-value ≥ 0.80). Again in 2007, PDDs by general medical practitioners differed significantly from other prescribers (Cohen's *d*-value = 1.01) and between the specialists and other prescribers (Cohen's *d*-value = 1.63). In 2009, high PDDs were observed in general medical practitioners compared to paediatricians (Cohen's *d*-value = 2.49); between the specialists and paediatricians (Cohen's *d*-value = 3.05); and between paediatricians and other prescribers (Cohen's *d*-value = 2.38). Finally, in 2010, the differences in the PDDs between the general medical practitioners and paediatricians were found to be practically significant (Cohen's *d*-value = 1.59); as well as that between the specialists and paediatricians (Cohen's *d*-value = 1.67) (refer to additional results). Although high doses prescribed for fluoroquinolones were observed by general medical practitioners, they could not be explored further to draw satisfactory conclusions as data for diagnoses were incomplete.

4.4 Limitations of study

The first limitation to this study was the inability to correlate antibiotic use with diagnoses as data in this regard were incomplete. Strom (2006:169) explained that most claims are reimbursed based on the right procedures taken during the outpatient encounter and not on the diagnoses. Furthermore, most general practitioners are not well motivated to provide diagnoses for a drug to be reimbursed (Strom, 2006:170); this may be true in the South African setting.

Secondly, it was not certain whether antibiotics were actually consumed by patients and

consequently may not actually reflect total antibiotic use in the population. The medicine claims data only furthermore provided information on outpatient encounters in the private health sector and medications reimbursed by the PBM company. Thirdly, medicines not covered by the medical aid and paid by the patient were excluded and consequently limits the scope of the empirical investigation. Lastly, the data field for the weight of patients was lacking in the database. This flaw affected the precise determination of the recommended daily doses (RDD) of fluoroquinolones in patients 18 years and younger.

Despite these limitations, this is the first study to be conducted in South Africa measuring fluoroquinolone use in adults according to the ATC/DDD classification system by the use of medicine claims data. Furthermore, it is the first study comparing the prescribed daily doses (PDD) to the recommended daily doses (RDD) of fluoroquinolones prescribed in patients 18 years and younger and the influence of the type of prescriber on the PDD in the private health sector of South Africa utilising medicine claims data. The South African private health sector has coverage of approximately 20% of the country's population, especially for those in employment. Medical aid schemes remain the main means of financing in the South African private health sector. The PBM company processes approximately 300 000 real-time and 30 000 doctor transactions daily. The reliability and validity of the data were ensured by gate-keeping services, eligibility services, utilisation management services, clinical management services and pricing management along with real-time benefit management (refer to paragraph 1.5.2.2.1).

According to Strom (2005:167), medicine claims databases are beneficial in pharmacoepidemiological studies with regard to providing large sample populations representative of the general population in the identification of rare events in drug use. This is evident in the use of fluoroquinolones in patients 18 years and younger. The use of information from the medicine claims database also provided a suitable denominator to describe fluoroquinolone employing the ATC/DDD methodology. Finally, recall or interviewer biases, which distort findings, were avoided in the study because of the use of medicine claims data.

4.5 Recommendations

From the study, the following recommendations are proposed:

- Effective interventions should be instituted nationwide to curb antibiotic use, particularly during the winter seasons, as a majority of upper respiratory tract infections may be of viral origin.

- Proper and effective infection control methods should be directed at Gauteng to reduce antibiotic use.
- It is also recommended that further studies be conducted to determine the future implications on the use of new broader-spectrum antibiotics such as amoxicillin/clavulanic acid, azithromycin and levofloxacin; and their evidence in proper infection control.
- The ATC/DDD methodology must be used to quantitatively measure antibiotic use in other health settings to enable comparison across different levels, e.g. the public and private health sectors.
- Further studies are recommended to identify the indication for use of fluoroquinolones such enoxacin, gemifloxacin, lomefloxacin, gatifloxacin and norfloxacin, which are not indicated in patients who are 18 years and younger.
- Interventions must be aimed at prescribers, especially general medical practitioners, to influence the prescribing habits with reference to prescribing unapproved fluoroquinolones in patients who are 18 years and younger.
- Prescribers should be encouraged to include the International Classification of Diseases (ICD)-10 diagnoses codes on prescriptions issued to facilitate future epidemiological studies.
- Finally, appropriate interventions should be instituted to educate prescribers on the recommended daily doses of fluoroquinolones approved in children.

4.6 Chapter summary

This final chapter completes the study by correlating the achievements of the study to the specific objectives outlined from the beginning of the study. The strengths and limitations were described, and recommendations for future research were made.

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ANNEXURE A – SUPPLEMENT TO CHAPTER 2

This supplement contains additional information to the literature review phase of the study (refer to chapter 2).

ANNEX. A.1 ATC systems main groups

A	Alimentary tract and metabolism
B	Blood and blood forming organs
C	Cardiovascular system
D	Dermatologicals
G	Genito-urinary system and sex hormones
H	Systemic hormonal preparations, excl. sex hormones and insulins
J	Anti-infectives for systemic use
L	Antineoplastic and immune-modulating agents
M	Musculo-skeletal system
N	Nervous system
P	Antiparasitic products, insecticides and repellents
R	Respiratory system
S	Sensory organs
V	Various

ANNEXURE B – SUPPLEMENT TO CHAPTER 3

This supplement contains information, tables and figures relevant to the empirical investigation of the study (refer to chapter 3).

Annex. C.1 Author Guidelines - Southern African Journal of Infectious Diseases

Manuscripts submitted to the SAJID must be in the form of *Research Articles, Brief Reports, Clinical Case Studies, Correspondence, Reviews, State-of-the-Art Articles, Commentaries and Opinion Papers, Editorials* or *Supplement Articles.* The Journal welcomes the publication of *Guidelines, Conference Proceedings Newsletters or Press Releases,* and *Book Reviews.* Articles, Brief reports and Reviews are peer reviewed; other categories are reviewed by the Editors. Commentaries and Editorials are generally invited contributions, indicating the authors' identity, while manuscripts in the form of Reviews, and State-of-the-Art Articles may also be requested by the Editors.

All manuscripts must have conflict of interest and funding statements. When authors submit a manuscript, whether an article or a letter, they are responsible for disclosing all financial and personal relationships that might bias their work. To prevent ambiguity, authors must state explicitly whether potential conflicts do or do not exist. Authors should do so in the manuscript on a conflict-of-interest notification page that follows the title page.

Manuscripts describing research in human subjects or animals must indicate ethics clearance from appropriate research review committees. When reporting experiments on human subjects, authors should indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.

Articles describe original investigations at an acceptable degree of completion, constituting an advance in the field. Articles must not exceed 3500 words of text, without counting the abstract, references or legends, and illustrations and tables must be limited to the minimum necessary for clear and concise presentation. The abstract must either be structured, using *Background, Methods, Results,* and *Conclusions* as headings and comprising no more than 250 words, or unstructured with a 200 word limit. Articles are limited to a maximum of 7

insets (tables and figures combined) and 50 references.

Brief Reports present complete studies that are narrower in scope than those described in Articles or that present new developments. Manuscripts that are descriptive or primarily methodological in nature, or that describe in vitro chemotherapeutic studies should, in general, be submitted as Brief Reports. Brief Reports include an abstract (no more than 100 words) and are limited to a total of no more than 2000 words of text, a total of 2 inserts (tables or figures), and 15 references.

Correspondence (letters) must be submitted in reference to a previous publication in SAJID (within the previous 12 months), or relate to a topical matter in line with the interests of FIDSSA, PHASA or their affiliated societies. Please prepare the letter in manuscript format, including a title page. The letter must not exceed 750 words of text, 1 insert (table or figure) and 10 references.

Commentaries and Editorials are generally invited by the Editor and are overviews of articles in SAJID, or of other research in epidemiology or infectious diseases, or matters relating to public health and other issues of special interest to FIDSSA, PHASA or their associated societies. Unsolicited commentaries are also considered.

Reviews and *State-of-the-Art Articles* that are research oriented or fall within the fields of interests of FIDSSA, PHASA or any of their affiliated societies will be considered for publication by SAJID. Prospective authors of such manuscripts are advised to communicate with the Editor in advance to ensure that a specific contribution is deemed appropriate and timely. Manuscripts of Reviews and State-of-the-Art Articles will be peer-reviewed.

Reviewers

The Journal would encourage authors to supply the names of at least 2 potential reviewers for their manuscript, as well as to indicate any reviewers they would feel may have a potential conflict of interest with regard to their submission.

Supplements

Requirements for supplement manuscripts generally follow those for SAJID manuscripts, including conflict of interest and funding statements. Inquiries relating to suitability of topic,

programme organisation, production and costs should be made to the Editor.

Evaluation of manuscripts

Review procedure. The Editor-in-Chief and Emeritus Editor screen all unsolicited manuscript submissions and some of these are rejected without further review. All other manuscripts are sent to a minimum of two outside experts for review. After receipt of the reviewers' reports, the Editor-in-Chief and the Emeritus Editor with administrative assistance of the Journal Secretary discuss the merits of the manuscripts and the Editor-in-Chief makes the final decision to accept, reject, or request revision of the manuscript. A request for revision does not guarantee ultimate acceptance of the revised manuscript

Related manuscripts. If there appears to be significant overlap between a manuscript submitted to SAJID and another submitted manuscript by the same authors to SAJID or another journal, the editors will take the matter up with the corresponding author, and based on the response, take appropriate action (ask for modification, or reject with detailed explanation). Further action may include informing the appropriate authority in the authors' resident institution and if overlapping is discovered after publication in SAJID, publishing an appropriate announcement to that effect in the journal.

DOCUMENT REQUIREMENTS

Checklist: The following are required for your manuscript to be processed:

Covering Letter

All manuscripts submitted to SAJID must be accompanied by a letter declaring that the manuscript has not been submitted or accepted for publication elsewhere. This letter must confirm and declare that all authors have seen and approved the content and have contributed significantly to the work. Authors should suggest potential unbiased reviewers who are qualified to review their manuscript. A covering letter must also accompany a revised submission and must address issues raised in the review process.

Manuscript Preparation

The SAJID complies with the Uniform Requirements for Manuscripts Submitted to Biomedical Journal Journals (*Ann Intern Med* 2000; 133:229-231

editorial]; **http://www.icmje.org**, full text). Text, tables, references, and legends must be double- spaced. Italics should be used for genus and species names and for genes but not for in vivo, in vitro, in situ, et al., or other Latin-derived expressions. For layout of manuscript and appropriate style see a recent issue of SAJID.

Title page. On the title page, please supply a running head of not more than 40 characters and spaces, a title of not more than 160 characters and spaces, the names and affiliations of all the authors, and word counts of the abstract and text. Each author's first name, subsequent initials and surname must be used.

Footnote page. Footnotes must include:

- Statement that authors either have or have not a commercial or other association that might pose a conflict of interest (e.g. pharmaceutical stock ownership, consultancy, advisory board membership, relevant patents, or research funding)
- Statement naming sources of financial support (including grant numbers)
- Name, date (month and year), and location (city, and country if not South Africa) of a meeting at which all or part of the information has been presented (include an abstract number, if available)
- Name, address, telephone and fax numbers, and e-mail address of the person to whom correspondence should be addressed
- Current affiliations and addresses for authors whose affiliations have changed since completion of the study

Abstract. The abstract for an Article may be structured with the headings Background, Methods, Results, and Conclusions (250-word limit) or unstructured (200-word limit). Abstracts of Brief Reports should be no more than 100 words. Whether structured or unstructured, the abstract must state the purpose of the research, the methods used, the results, and the conclusions. Do not cite references in the abstract. Include up to 10 key words, separate from the abstract. Please remember that the abstract is particularly useful for literature retrieval purposes.

Text. The text of Articles must be no longer than 3500 words, and that of Brief Reports no longer than 2000 words. The Methods section must include a statement that informed consent was obtained from patients or their parents or guardians, and human experimentation guidelines of the National Department of Health (http://www.doh.gov.za) or

the South African Medical Research Council (MRC; http://www.sahealthinfo.org/ethics/index.htm) and /or those of the authors' institution(s) were followed in the conduct of clinical research or that animal experimentation guidelines (see MRC website above) were followed in animal studies.

References. Articles are generally limited to 50 references, Brief Reports to 15 references. Only works that have been published or accepted for publication can be included in the reference list. Unpublished observations by the authors (authors' unpublished data) personal communications (SP Stanley, personal communication), and manuscripts submitted for publication (J Odendaal, S Coovadia and J Radebe, submitted) should be mentioned parenthetically in the text Please number references in order of appearance; those cited only or first in tables or figures are numbered according to the order in which the table or figure is cited in the text. Example: If table 3 is cited in the text after reference 20, a new reference cited in table 3 will be reference 21.

References must follow the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org, full text). Provide all authors' (or editors') names when there are fewer than 7; for 7 or more, list the first 3 and add "et al." Titles of journals not listed in *Index Medicus* should be spelt out in full. Reference to a doctoral thesis or Master's dissertation should include the author, title, institution, location, year and publication information, if published. For online resources, include a URL and date accessed. Accuracy of references is the responsibility of the authors.

Examples of the proper format are as follows:

Sonnenberg P, Glyn Thomas R, Glynn JR, Shearer S, Godfrey-Faussett, Murray J. Clinical and radiological features of pulmonary disease due to culture-positive Mycobacterium tuberculosis or non-tuberculous mycobacteria in South African gold miners. South Afr J Epidemiol Infect 2005; 20: 130-135

Marin M, Nguyen HQ, Langidrik JR, et al. Measles transmission and vaccine effectiveness during a large outbreak on a densely populated island: Implications for vaccination policy. Clin Infect Dis 2006; 42: 315-319

Strebel PM, Papania MJ, Halsey NA. Measles vaccine. In: Plotkin SA, Orenstein WA, eds. Vaccines. 4th ed. Philadelphia: WB Saunders, 2004: 389-440.

Mothibeli KM, McGee L, Smith AM, Klugman KP. Molecular epidemiology of pneumococcal serotype 3 isolates.[abstract ID P56]. In: Programme and Abstract Book of the 1st Joint Congress of the Federation of Infectious Diseases Societies of Southern Africa (Sun City, North-West Province). Johannesburg: Presentations Graphics, 2005: 42.

World Health Organization. Initiative for vaccine research. Available at: http://www.who.int/vaccine_research/diseases/measles/en/. Accessed 1 February 2005.

Acknowledgment(s). The page preceding the references may include a statement thanking those who assisted substantially with work relevant to the study.

Statistical analysis. The statistical analyses used should be identified both in the text and in all tables and figures where the results of statistical comparison are shown.

Units of measure. All Data should be expressed in metric units; use of SI units is encouraged. Use ºC for temperature.

Tables and figures. Articles are limited to a maximum of seven inserts (tables and figures combined), Brief Reports to a maximum of two inserts. Data should not be repeated in both a table and a figure. Abbreviations and acronyms used in tables and figures must be explained in the table footnotes and figure legends, even if already defined in the text.

Tables should be numbered in the order of mention in the text. Tables should be typed double-spaced throughout, with no vertical or internal rules. Footnotes and accompanying explanatory material should be kept to a minimum. Footnotes should be placed below the table and designated by superscript lowercase letters (listed in order of location when the table is read horizontally). Each column must have an appropriate heading describing the data in the column below, and units of measure must be clearly indicated. For further instructions on the preparation of tables in Word , consult the Special Instructions for Tables.

Figures should be also numbered in the order of mention in the text and should appear at the end of the manuscript and references. Your figures should be prepared in accordance with the Guidelines for Submission of Artwork. Letters, numbers, and symbols should be clear and of sufficient size to be legible when the figures are reduced. Photomicrographs should have internal scale markers. Figures reproduced from other publications must be accompanied by permission from the copyright holder. If the manuscript is accepted, the

author will be required to send one complete set of glossy, hard-copy figures.

Figure legends should be double-spaced and appear on a separate page preceding the figures. Any abbreviations or symbols used but not defined in the figure itself must be defined in the legend.

Style. Authors are referred to the *American Medical Association Manual of style: A Guide for Authors and Editors* (9th ed., Williams& Wilkins, 1997) and the *Chicago Manual of Style* (15th ed., University of Chicago Press, 2003).For commercially obtained products mentioned in the text, list the full names of manufacturers. Generic names of drugs and other chemical compounds should be used.

Nomenclature. SAJID recommends the latest widely accepted nomenclature, as set out in documents prepared by recognised international agencies e.g. the *International Journal of Systematic and Evolutionary Microbiology, Bergey's Manual of Determinative Bacteriology* (9th ed., revised, Williams& Wilkins, 1993), *Virus Taxonomy – The Classification and Nomenclature of Viruses: Sixth Report of the International Committee on Taxonomy of Viruses* (Springer-Verlag, 1995). The latter document also supplies standard abbreviations for virus species.

Clinical trials registration. All clinical trials must be registered in a registry that is electronically accessible to the public, free of charge. Registration should occur before patient enrolment and the registry's URL and the trial's registration number must be supplied at the end of the manuscript's abstract. For information on acceptable registries, consult the ICMJE Web site, http://www.icmje.org . The National Library of Medicine's registry which is free and open to all investigators, generally meets with the requirements of journals for the publication of clinical trials.

Annex. B.2 Author guidelines – Journal of antimicrobial chemotherapy

Article types and format

All documents should be double spaced, with wide margins. A clear, legible single font (which is readily available internationally) and point size should be employed throughout. For symbols, please use the 'insert symbol' function and ONLY select characters from the 'normal text' subset. All submitted articles should be line numbered (using continuous line numbers). To do this in Word, use File, Page Setup, Layout, Line Numbers and select continuous line numbering. Please DO NOT insert page numbers (as the pdf proof created by the online submission system will automatically be page numbered).

All articles should include a title page comprising: article title; author names and their affiliations (each affiliation address must be given separately and in full); telephone, fax and e-mail contact details for the corresponding author; a short running title; and 3-5 keywords (very general terms such as 'bacteria' and 'human' and terms already present in the title should be avoided, as should non-standard abbreviations). In addition, all articles must include a Funding section (if reporting original research) and a Transparency declarations section.

Original articles and Brief reports must have a structured synopsis. The headings for the structured synopsis are as follows: Objectives, Patients and methods (or Methods), Results, and Conclusions.

Original articles. There is no length limit for this format; however, papers must be written as concisely as possible. Original articles are divided into the following sections: Synopsis (250 words maximum), Introduction, Materials (or Patients) and methods, Results, Discussion, Acknowledgements, Funding, Transparency declarations and References. Repetition of content between sections must be avoided. A combined Results and Discussion section is acceptable.

Brief reports. These should have the same format as Original articles, but should have no more than two figures/tables, should have a maximum of 20 references and should not exceed 1500 words of text.

Antimicrobial practice. Articles on topics related to the use of antimicrobials, format as for Original articles/Brief reports.

Correspondence. Letters on topics of concern or interest in the field of antimicrobial chemotherapy, particularly arising from papers or letters already published in the Journal. These should be addressed to the Editor-in-Chief and must not exceed 800 words, one figure or table and 10 references.

Case reports. JAC will publish Case reports that are of sufficient calibre and potential importance, and they should be submitted in the form of Correspondence (see above). Please note that patient anonymity MUST be preserved in Case reports (see the later section on Ethics approval and patient consent/privacy).

Systematic review articles. There is no length limit for this format. A systematic review, as defined by the Cochrane Handbook, is 'A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarize the results of the included studies.' They should include a structured synopsis (with appropriate headings; these may differ from the headings used for Original articles etc.).

Review articles. There is no length limit for this format. These generally aim to give an overview of a field suitable for a wide audience, and they should include a synopsis (250 words maximum). Most reviews are invited. We are pleased to consider unsolicited reviews, but authors are encouraged to consult the Editor-in-Chief in advance of writing to avoid duplicating commissioned material.

Leading articles. These are usually in the region of 800-1000 words and may contain the expression of opinion as well as fact. They should address a topical subject, perhaps taking a particular viewpoint and throwing new light on a current debate. A leading article should include a short synopsis (150 words maximum) that should convey the topics and ideas the article covers. Those wishing to contribute a Leading article are encouraged to contact the Editor-in-Chief to discuss their ideas before writing to prevent clashes with any articles already in the pipeline.

Please note that on publication all Original articles and Brief reports, as well as Antimicrobial practice papers, will be published under the heading of Original research so that articles on similar topics can be grouped together when assigned to an issue. In addition each piece of Correspondence will be published as either a Research letter or a Letter to the Editor.

Peer review

After preliminary examination of the submission by Editorial Office staff to check that all the necessary elements are present, the paper is passed to the Editor-in-Chief. The Editor-in-Chief then assigns the paper to an appropriate Senior Editor. The Senior Editor is then responsible for selecting an Editor to handle the article. Articles can be rejected immediately by the Editor-in-Chief, a Senior Editor or an Editor without further peer review. The assigned Editor is responsible for selecting referees and obtaining referee reports. The usual number of referees is two, however, the Editors reserve the right to make a decision on a paper on the basis of one referee report, or seek the opinion of more than two referees if they judge this to be necessary or desirable. Leading articles and Correspondence are not routinely sent for external refereeing, but the Editor-in-Chief, Senior Editors and Editors reserve the right to seek the opinion of one or more external referees if they judge this to be necessary or desirable. Senior Editors, Editors and referees are asked to consider whether they have any conflicts of interest when they are assigned a paper, and if necessary to decline to handle the paper. See the section 'Conflicts of interest' for more information on this subject.

If an Editor decides upon rejection of a paper, it is passed back to the handling Senior Editor for approval of this decision. All rejection correspondence therefore originates from a Senior Editor. Authors should regard rejection as final and only resubmit if they have been invited to do so. Papers may be rejected for a number of reasons, including: (i) they may be of only peripheral interest and perhaps more suitable for submission to a different journal; (ii) they may be, in the opinion of the reviewers, scientifically flawed; (iii) they may be unclear or overly long; or (iv) they may not make a significant contribution to the literature. Requests that a revised version of a paper be submitted for consideration are sent direct to the corresponding author from the Editor responsible. Any revised version should be submitted within 6 weeks of the revision request or the Journal reserves the right to consider the manuscript as a new submission that may be subject to further refereeing.

The Editor-in-Chief, Senior Editors and Editors reserve the right to request more rounds of revision and resubmission/refereeing, or reject a paper outright, if they judge that any revised version does not adequately address the concerns raised by the referees and the Editor. Once the Editor is satisfied that a revised version has adequately dealt with any points raised they may accept the paper.

Authors can appeal against a decision by contacting the handling Senior Editor, but unless

there has been a gross misunderstanding of the submitted article by the Editor and referees, rejection appeals are not likely to be successful. Authors should appreciate that if they resubmit an article that has been rejected without substantially modifying it in line with the suggestions of the Editor and referees, it is almost certain to be rejected again.

After acceptance the paper is sent for copy-editing and typesetting prior to production of proofs for author correction.

The Journal maintains the right to edit any paper to the extent necessary to achieve clarity and precision of expression and to conform with English usage and the Journal's conventions. Please note that if authors ignore requests to conform with Journal style at the revision stage, these changes may be enforced during copy-editing and proof production.

Articles submitted by Editors of the Journal

JAC does not bar Editors (including Senior Editors and the Editor-in-Chief) from submitting articles to the Journal. Articles submitted by Editors are handled in the same fashion as other articles subject to the following considerations: these articles are never assigned to the submitting Editor, or an Editor from the same institution; the submitting Editor is unable to access details of their article through the online submission system; and, like other authors, the submitting Editor will not know the identity of the handling Editor (in cases of rejection) or referees.

Supplement articles

Supplement articles are subject to peer review and may be rejected. Unless specialist external expertise is required, this peer review is conducted among the team of Editors that is dealing with the Supplement.

Proofs

An e-mail containing a link to the proof is sent to the corresponding author. The proof should be read carefully, paying particular attention to any tables, figures and references, and corrections (and answers to any queries) should be submitted to the *JAC* Editorial Office as soon as possible. Authors should pay particular attention that they check any dosage directions, owing to the seriousness of any error entering the printed record. Extensive changes at the proof stage are not permitted. Authors may be charged for correction of their non-typographical errors. The Journal reserves the right not to comply with changes marked on the Author's proof if these are contrary to the style set down in the Instructions to Authors. In the event of important developments in a field that affect the paper arising after the final

revision, a 'Note added in proof' may be permitted. Please note that Supplementary data files are largely unedited and are not proofed out.

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Journal policies

Material offered for publication must be original, unpublished and not under simultaneous consideration by another journal. Any previous publication of the material (including abstracts in conference proceedings or posters, or in a clinical trials results database) must be declared in the covering letter, as well as in the Acknowledgements section of the paper. For these purposes the posting of essentially raw data on a website without significant analysis, is not considered to represent prior publication. In addition, authors must include in the covering letter details of ANY previous submission of the work to *JAC* that has been rejected. The manuscript number of the earlier submission must be provided, as well as a point-by-point response to the comments made in the decision e-mail for the previous

submission.

Authors should not fragment their research into least publishable units. Authors must be aware that *JAC* may decline to publish articles if this approach becomes evident. Authors are fully responsible for the accuracy of all data in their articles. *JAC* reserves the right to use plagiarism detection software on any submitted material. *JAC* is a member of the Committee on Publication Ethics (COPE), and strives to adhere to its code of conduct and guidelines. For further information see http://www.publicationethics.org.uk/. Authors are also expected to behave ethically and unacceptable practices include: (i) plagiarism; (ii) fabrication or falsification of data; (iii) omission of legitimate authors, Funding information or financial conflicts of interest; (iv) inclusion of authors who have not made a significant contribution to the design and execution of the work described; and (v) redundant/duplicate publication.

In-press papers or papers under editorial consideration

In-press and submitted papers that are important for the review of a paper MUST be uploaded when the paper is submitted and referred to in the covering letter that accompanies the submission. Authors should be aware of the issues of redundant/duplicate publication. For further information, please see the following Editorial: Reeves DS, Wise R, Drummond CWE. Duplicate publication: a cautionary tale. *J Antimicrob Chemother* 2004;**53**: 411-2.

Sequence data

When reporting sequences they must be submitted to one of the three major databases and an accession number must be provided before publication.

If a sequence has been submitted but an accession number has not yet been provided or the sequence is not yet available to the public then authors must submit the annotated submission PDF file (or .txt or .docx file). If a PDF file is submitted then authors must also provide the .txt or .docx file so that the Editor and referees can analyse it.

Supplementary data

Please note that it is also possible to submit files containing Supplementary data. The Supplementary data (for example large tables of MICs, or a questionnaire) can be lodged with the version of the paper published online as an extra resource for readers. Supplementary data is largely unedited and is not proofed out so authors should ensure that they provide high quality, accurate files. In addition, authors must ensure that they cite the Supplementary data within the article. Please contact the Editorial Office if you would like further details.

Authorship

The authorship of the paper should be confined to those who have made a significant contribution to the design and execution of the work described. In the case of clinical trials/randomized control trials it is compulsory for the contribution of each author to be clearly stated in the Transparency declarations section, after the information on conflicts of interest. Authors of other types of article may indicate the contribution made by each author if they wish.

JAC recommends that authors review the ICMJE criteria for authorship before submission (http://www.icmje.org/#author).

Author signed submission forms

When submitting a paper online authors should simultaneously provide a written statement, signed by all the authors indicating that they have complied with the stipulations in the Instructions to Authors (the statement MUST include the title of the paper and the COMPLETE list of authors). A copy with the original signatures must be scanned and e-mailed (preferred) or faxed to the Editorial Office as soon as possible after online submission (jac@bsac.org.uk/+44-121-212-9822). A blank form is available at http://www.oxfordjournals.org/jac/for_authors/signature.pdf. If at any stage during consideration the authorship of the article changes, the authors must supply a signed statement from ALL the authors (including any whose names are being removed) explicitly indicating the nature of the changes and their agreement.

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The author list of any submission should be decided upon and fixed BEFORE submission. Other than in exceptional circumstances the Journal does not allow addition or removal of author names after submission. A satisfactory explanation for any proposed changes in authorship will be required and ALL authors will be required to supply new signed consent forms that reflect the changes. We will also require a signed consent form from any person whose name has been removed indicating that they agree to the removal of their name from the author list. Owing to the complexity of these rules we strongly advise authors to fix the author list before submission and not to attempt to make changes later.

'Umbrella' groups and authorship

Many large collaborative studies (frequently resistance surveys) are organized under a group name that represents all of the participants. *JAC* will not accept a group name as an 'author' of an article. All articles must have at least one named individual as author. Authors of large collaborative studies should list the author(s) of the article and follow this with 'on behalf of the GROUP NAME'. The names of all of the participants should then be listed in the Acknowledgements section.

Professional medical writers and editorial assistance

Professional medical writers and other forms of writing assistance have an important role to play in the clear communication of scientific results. However, unless this role is openly explained and acknowledged unfounded suspicions about this role will continue. *JAC* encourages the open and precise description of any such assistance received by authors in relation to any article. It is possible that writers may qualify for authorship of a manuscript, we recommend that authors review the ICMJE criteria for authorship before

submission (http://www.icmje.org/#author).

The precise role of the writer or service in the origin or preparation of the manuscript must be declared in the Transparency declarations section; we recommend that the name of the writer (and their agency where applicable) or the service is provided. If this support was funded, the source must be declared in the Funding section.

Responsibilities of the corresponding author

For each paper submitted to *JAC* there must be a single corresponding author. As the representative of the authors, the corresponding author must ensure that all authors are given access to submitted and revised versions of papers. The corresponding author is responsible for the collation of the authors' signatures on submission letters and also the collation and communication of proof corrections to the Journal. The corresponding author should be the signatory of the publication licence form. As the authors' nominated representative, the corresponding author will be held primarily accountable for any failure to comply with the Instructions to Authors or generally accepted standards of good practice. This does not absolve other authors of responsibility, however.

The corresponding author will act as the primary contact for correspondence regarding the paper, and as such authors should take care not to appoint a corresponding author likely to be absent for extended periods (such as a sabbatical) during the consideration of the paper as this is likely to cause unacceptable delays.

Please note that papers submitted via ScholarOne Manuscripts must be submitted through the account of the corresponding author listed on the paper, not through the account of one of the other authors or the account of a third party who is not on the author list. This is to ensure that there can be no argument regarding the identification of the corresponding author. In addition, the authors listed during the submission process on the ScholarOne Manuscripts website must fully match the author list of the actual submitted article.

Research involving humans

Authors must indicate in the Methods whether the research was conducted in accordance with the Declaration of Helsinki and national and institutional standards. If approval was obtained from an Ethics Committee the authors should indicate this, as well as any approval/reference number. Written informed consent must be obtained from study participants and the existence of this consent must be stated in the article.

Patient privacy

Patients have a right to privacy. Any information that might result in identification of individuals must be omitted, especially if it is not directly clinically relevant. Patient age, sex, admission dates and co-morbidities should be removed as far as possible. If it is possible that a patient could be identified, the authors must obtain written informed consent from the individual(s) concerned and state that this has been obtained in the article. Publication consent forms should be retained by the authors and not supplied to the Journal. If the patient is deceased the next of kin should be contacted. If consent cannot be obtained the authors must explain the circumstances briefly in the article, as well as in detail in the covering letter. In rare circumstances where relevant clinical details mean that the patient can be identified, the patient/next of kin must be shown the manuscript before submission and made aware as part of the informed consent process that the article may appear on the internet.

Research involving animals

Authors must state their compliance with relevant institutional and national standards for animal care and experimentation, together with the details of any authorities that licensed the experiments.

Funding

ALL papers submitted to *JAC* reporting original research MUST include a ‘Funding’ section. This section should appear after the 'Acknowledgements' section. Details of all funding sources for the work in question must be given. Authors must list any internal funding. If no specific funding has been received then this should be clearly stated; equally if data have been generated as part of the routine work of an organization, this too should be stated. On-going financial support for any of the authors should also be included under the Funding heading. If a professional medical writer or similar service was involved in the origin or preparation of a manuscript and this support was funded, the source must be declared in the funding section.

Sources of funding may of course still be thanked in the Acknowledgements section, but should not be listed again in the Transparency declarations (see below), unless there is an important reason for doing so. For example if the funder played any decision-making role in

the research this must be stated.

The following rules should be followed:

- The sentence should begin: ‘This work was supported by …’
- The full official funding agency name should be given, i.e. ‘the National Cancer Institute at the National Institutes of Health’ or simply 'National Institutes of Health' not ‘NCI' (one of the 27 subinstitutions) or 'NCI at NIH’ (full RIN-approved list of UK funding agencies is at http://www.rin.ac.uk/files/List-of-major-UK-research-funders.pdf)
- Grant numbers should be complete and accurate and provided in brackets as follows: ‘(grant number ABX CDXXXXXX)’
- Multiple grant numbers should be separated by a comma as follows: ‘(grant numbers ABX CDXXXXXX, EFX GHXXXXXX)’
- Agencies should be separated by a semi-colon (plus ‘and’ before the last funding agency)
- Where individuals need to be specified for certain sources of funding the following text should be added after the relevant agency or grant number 'to (author initials)'.

An example is given here: ‘This work was supported by the National Institutes of Health (P50 CA098252 and CA118790 to R. B. S. R.) and the Alcohol & Education Research Council (HFY GR667789).

Conflicts of interest

Conflicts of interest have the potential to affect authors, referees and Editors (including Senior Editors and the Editor-in-Chief). *JAC* has the following systems in place to deal with conflicts of interest:

Authors. Authors are required to include a Transparency declarations section in every submission to the Journal (for details see below).

Referees. When invited to act, and again when they agree to act, referees are reminded to consider whether they have any potential conflicts of interest. Referees are asked to discuss any perceived potential conflict with the Editor of the article who will reach a decision as to whether it is appropriate that the referee acts on the article or whether they should withdraw.

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In the interests of openness, ALL papers submitted to *JAC* MUST include a 'Transparency declarations' section (which should appear at the end of the paper, before the 'References' section). We suggest authors concentrate on transparency declarations (i.e. conflicts of interest) of a financial nature, although relevant non-financial disclosures can also be made. Authors should consider making a declaration if they answer 'Yes' to any of the following questions:

1. Have you in the period of research leading up to this publication accepted any of the following from an organization (including government departments or granting bodies) that may in any way be financially affected by the conclusions of your article (e.g. reimbursement for attending a symposium, a fee for speaking, a consultancy fee, funds for research other than directly for this work, funds for a member of staff, any other substantial material benefit)?

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4. Have you received the assistance of a professional medical writer or similar service? [The precise role of the writer or service in the origin or preparation of the manuscript must be declared and we recommend that the name of the writer (and their agency where applicable) or the service is provided.]

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Authors should either include appropriate declarations or state ‘None to declare’. Importantly, the declarations should be kept as concise as possible, should avoid giving financial details (e.g. sums received, numbers of shares owned etc.), and should be restricted to declarations that are specific to the paper in question. Authors will of course need to consider whether or not the transparency declarations need to be amended when revisions are submitted.

The burden of responsibility rests with all authors, who must ensure that appropriate declarations are included. The corresponding author will be responsible for obtaining the relevant information from all of their co-authors. By signing a submission form each author is stating that they have made any necessary transparency declaration. All authors should carefully consider the embarrassment and potential damage to their reputation that could result should they fail to declare an interest that is revealed subsequently.

If only some authors need to make a declaration it must be made clear that the remaining authors have nothing to declare, for example:

'A.B. has received funds for speaking at symposia organized on behalf of Panacea Ltd and has also received funds for research from Panacea. C.D. is a member of the Panacea advisory board for fantastazole. All other authors: none to declare.’

All papers submitted to *JAC* must include a transparency declarations section; papers that do not include such a section will not enter the review process; they will be returned to the corresponding author so that the appropriate section can be added. Following resubmission the paper will then be progressed to peer-review.

In the case of clinical trials/randomized control trials it is compulsory for the contribution of each author to be clearly stated in the Transparency declarations section, after the information on conflicts of interest. Authors of other types of article may indicate the contribution made by each author if they wish.

Other useful information

In some instances (often when the authors themselves have no interests to declare) it may be helpful to readers as background information to give brief details of organizations that do

have an interest but do not appear elsewhere in the article, for example ‘Fantastazole is owned by Wonder Pharmaceuticals’.

Misconduct

We will energetically pursue accusations of misconduct directed at authors, Editors or referees and have a number of sanctions at our disposal including the option to inform employers about accusations and ask them to mount their own internal investigations. Accusations should not be made lightly or in the absence of the likelihood of supporting evidence being obtainable. The Journal may take the view that accusations are malicious if supporting evidence cannot be found and may direct sanctions against accusers in such cases. Any accusation of misconduct should be addressed to the Editor-in-Chief (unless it involves the Editor-in-Chief, in which case it should be directed to the Chairman of the Advisory Board). *JAC* is a member of COPE and will follow its guidelines on the handling of investigations into research misconduct.

Clinical trials/Randomized controlled trials

Registration and data publication

Authors must register their trials in one of the databases dedicated to registration of trials. In addition, authors must state the database and provide the unique registration number – both in the abstract and in the main body of the paper.

JAC will consider for publication clinical trials for which there has been prior publication of trial data in results databases (such as http://www.clinicalstudyresults.org/about/ or others), however, authors MUST declare in the covering letter and the Acknowledgements section of the article that they have previously published data in a results database.

Contributions

The contribution of each author must be clearly stated in the Transparency declarations section, after the information on conflicts of interest.

Reporting standards

All involved in the publication of health intervention research have a duty to patients and society at large to ensure that this research is reported in a complete, accurate and transparent fashion. This includes authors, referees, Editors and Journals. *JAC* takes this responsibility seriously and endorses the work of organizations such as the EQUATOR network (http://www.equator-network.org/), an international initiative that seeks to improve the reliability and value of the medical research literature. There is a wide range of reporting guidelines, each specific for different types of study. Some of those for study types that are frequent in *JAC* are mentioned specifically below. Authors should consult the EQUATOR network website (http://www.equator-network.org/) for links to the latest versions of guidelines, which are organized by the study type.

Randomized controlled trials

Authors should comply with the Consolidated Standards of Reporting Trials (CONSORT) statement (www.consort-statement.org/) and use the resources within it (for example the checklist and flow diagram) to ensure they have addressed potential criticisms and provided all necessary information. Authors should include a CONSORT flow diagram in their article, and provide a copy of the completed checklist.

Systematic reviews and meta-analyses

For systematic reviews and meta-analyses of randomized controlled trials authors should comply with the PRISMA statement (which replaces the QUORUM statement), which consists of a checklist and flow diagram (http://www.prisma-statement.org/index.htm). Authors should include a PRISMA flow diagram in their article, and provide a copy of the completed checklist.

Outbreaks and intervention studies in nosocomial infection

Authors should comply with the ORION statement (www.idrn.org/orion.php), which is the CONSORT equivalent for infection control studies. Its purpose is to increase the quality of research and reporting in the area of nosocomial infection.

Economic evaluations

Authors of articles describing economic evaluations of antimicrobial interventions are encouraged to make use of the following resources, where applicable, in order to ensure that their work is both optimal and adequately described.

International Society of Pharmacoeconomics and Outcomes Research (ISPOR) Checklist for retrospective database studies, which can be accessed at:http://www.ispor.org/workpaper/healthscience/ret_dbTFR0203.asp. Quality of Health Economic Studies (QHES) Instrument. See Table 1 in:http://www.amcp.org/data/jmcp/Formulary Management-53-61.pdf

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JOURNAL STYLE

General

In addition to reading the information provided here, authors should consult a recent issue of the Journal for the layout and conventions used. The past tense should be used throughout for description of the results of the paper, the present tense should be used when referring to previously established and generally accepted results. Where possible, SI units should be used. Please ensure that characters with a similar appearance are consistent throughout the document and not from different Unicode sub ranges as with the Greek Delta.

Language editing

Particularly if English is not your first language, before submitting your manuscript you may wish to have it edited for correct usage of English. This is not a mandatory step, but may help to ensure that the academic content of your paper is fully understood by journal editors and reviewers. Language editing does not guarantee that your manuscript will be accepted for publication. If you would like information about one such service provided by SPi, please click http://www.oxfordjournals.org/for_authors/language_services.html. There are other specialist language editing companies that offer similar services and you can also use any of these. Authors are liable for all costs associated with such services.

Spelling

British spelling should be used. Spelling should follow that of the *Oxford Dictionary for Scientific Writers and Editors* and where this gives no guidance the *Concise Oxford Dictionary*. Spelling of drug names should conform with that given in the latest edition of the *British National Formulary* (published by the British Medical Association and the Royal Pharmaceutical Society of Great Britain and available online athttp://www.bnf.org/bnf), but please note that *JAC* will continue to use methicillin (not meticillin).

Abbreviations

Non-standard abbreviations should be defined at the first occurrence and introduced only where multiple use is made. See here for abbreviations that may be used without definition, as well as antimicrobial abbreviations (which may be used in Tables and Figures).

Dosage and routes of administration

Dosage frequencies should be given in full in English at each occurrence. Abbreviations are not permitted. Routes of administration other than intramuscular (im) and intravenous (iv), which may be abbreviated after definition, should be given in full in English.

MICs

Please note that all MIC data in *JAC* must be expressed in terms of mg/L (not μg/mL).

Bacterial nomenclature

When genus and species are given together use a capital letter for the genus and a lowercase letter for the species and italicize both e.g. *Staphylococcus aureus*. After the initial use in the text of the full name of an organism the generic name should then be abbreviated to the initial letter, e.g. *E. coli*. When the genus is used as a noun or adjective use lowercase roman unless the genus is specifically referred to e.g. 'staphylococci and streptococci' but 'organisms of the genera *Staphylococcus* and *Streptococcus*'. The name of an order has an initial capital but is not italicized, e.g. Enterobacteriaceae. For genera in the plural, use lowercase roman, e.g. salmonellae. When the species is used alone use lowercase e.g. viridans streptococci. For trivial names, use lowercase roman e.g. meningococcus. Authors should use bacterial names present in the *Approved List of Bacterial Names, Amended Edition* (1989), Skermanm, V.B.D., McGowan, V. & Sneath, P.H.A., Eds, ASM Press,

Washington, DC, USA (ISBN 1-55581-014-4), with subsequent alterations validly published by announcement in Validation Lists of the *International Journal of Systematic and Environmental Microbiology* (formally the *International Journal of Systematic Bacteriology*). A full list of validly published bacterial names is given at http://www.bacterio.cict.fr/allnames.html

Genetic and amino acid nomenclature

Bacterial genetics. Genotype designations are indicated with italic lowercase three-letter locus codes (e.g. *par*,*his*, *ara*). If several loci are involved in a related function the individual loci are designated by the addition of an uppercase italic letter to the locus code (*parC*, *ompF*). Phenotype designations (for example the protein product of a bacterial gene) are given in roman type with an initial capital letter (OmpF, LacZ). Erythromycin gene nomenclature should follow that described in: Roberts MC, Sutcliffe J, Courvalin P, Jensen LB, Rood J & Seppala H. Nomenclature for macrolide and macrolide-lincosamide-streptogramin B resistance determinants. *Antimicrob Agents Chemother* 1999; **43**: 2823-30.

Yeast genetics. Wild-type alleles are all uppercase and italicized (*LEU2*), mutant alleles are all lowercase and italicized (*leu2*), and gene products are capitalized on the first letter and are not italicized (Leu2).

General. Authors should ensure that they confine discussion of changes in amino acid sequence to the context of the protein (e.g. OmpF) and nucleotide changes to the context of the gene (e.g. *ompF*). Please also be aware of the difference between a mutant (a strain with one or more mutations) and a mutation (a change in the sequence of the genetic material).

Amino acids. The full residue names or three-letter abbreviations are preferred in the text (e.g. a methionine residue at position 184 should be symbolized Met-184). The single letter codes may be used in figures. Amino acid changes should be designated Met-184→Val or M184V.

When comparing nucleotide or amino acid sequences authors should exercise care in the use of the term homology. Homology should only be used when a common evolutionary origin is being implied; it is incorrect to give a percentage homology between two sequences. The wing of a bird and the human arm are homologous structures (they are believed to have a common evolutionary origin), homology cannot be quantified. For sequence comparison authors should use the terms identity and similarity. Sometimes 'equivalent' or 'counterpart' is more appropriate than 'homologue'.

Beta-lactamase nomenclature

Authors submitting articles reporting the identification of new beta-lactamases must provide evidence that they have contacted the relevant clearinghouse (http://www.lahey.org/Studies/ to deposit the new sequence data and receive a unique designation for the new enzyme.

Macrolide-lincosamide-streptogramin resistance determinant nomenclature

Nomenclature for macrolide-lincosamide-streptogramin resistance determinants should follow the structure suggested by: Roberts MC, Sutcliffe J, Courvalin P *et al*. Nomenclature for macrolide and macrolide-lincosamide-streptogramin B antibiotic resistance determinants. *Antimicrob Agents Chemother* 1999; **43**: 2823-30. A new gene must have ≤79% amino acid identity with all previously characterized MLS genes before receiving a new unique name. Adding subscripts or superscripts to established genes is not acceptable. See:http://faculty.washington.edu/marilynr/. Before submitting a sequence to GenBank or submitting a manuscript for publication, please contact Professor Marilyn Roberts (marilynr@u.washington.edu). Once a new name has been assigned you must indicate in your article that you have received approval by the nomenclature centre for the new gene name.

Tetracycline resistance determinant nomenclature

Nomenclature for tetracycline resistance determinants should follow that suggested by: Levy SB, McMurry LM, Barbosa TM *et al*. Nomenclature for new tetracycline resistance determinants. *Antimicrob Agents Chemother*1999; **43**: 1523-4. A new gene must have ≤79% amino acid identity with all previously characterized *tet* genes before receiving a new unique name. Adding subscripts or superscripts to established genes is not acceptable. See: http://faculty.washington.edu/marilynr/. The Levy Group is responsible for coordinating the naming of new *tet* genes and before submitting a sequence to GenBank or submitting a manuscript for publication, please contact Laura McMurry (laura.mcmurry@tufts.edu). Once a new name has been assigned you must indicate in your article that you have received approval by the nomenclature centre for the new gene name.

qnr gene/allele nomenclature

Authors submitting articles reporting the identification of new *qnr* genes or alleles must provide evidence that they have contacted the relevant clearinghouse (http://www.lahey.org/qnrStudies/) to deposit the new sequence data and receive a unique designation. Authors should consult Jacoby G, Cattoir V, Hooper D *et al*.*qnr* gene nomenclature. *Antimicrob Agents Chemother* 2008; **52**: 2297-9.

FICI data

Fractional inhibitory concentration index (FICI) experiments are performed in order to study drug interactions and they must be interpreted in the following way:

FICI<=0.5 = synergy

FICI>4.0 = antagonism

FICI>0.5-4 = no interaction

For further information please see the following Editorial:

Odds FC. Synergy, antagonism, and what the chequerboard puts between them. *J Antimicrob Chemother* 2003;**52**: 1.

Microarray data

Authors of articles containing microarray data must ensure that the full datasets are lodged with an appropriate publicly available online database (the data must not be supplied for publication as Supplementary data alongside the article). The data should be supplied with the submitted article if they are not already publicly available. The name of the database and the accession numbers should be provided in the article. Authors must ensure that their data are available for public scrutiny from the online publication date of their article at the latest.

Chemistry

General nomenclature. The IUPAC recommendations on chemical nomenclature should be followed (*IUPAC Compendium of Chemical Terminology* (1987, ISBN 0 632 01767 8, Blackwell Scientific Publications, Oxford). All chemical names are run together except those

of acids, acetals, esters, ethers, glycosides, ketones and salts, which are printed as separate words; hyphens are used to separate numbers, Greek letters and some configurational prefixes, e.g. *p*-nitrophenol. Italics are used for certain prefixes, e.g. *cis*-, *trans*- and *N*. Small capitals are used for dextro- and laevo- prefixes, e.g. L-glutamine.

Drugs. Spelling of drug names should conform with that given in the latest edition of the British National Formulary. Chemical or generic names of drugs should be used; trade names may be referred to once only upon first use of the generic or chemical name. The content of proprietary formulations should be given if relevant. Generic names should not be abbreviated in the text; abbreviations may be used in Tables if there is limited space. If compounds are referred to by code name or company number either the structure or a reference to a paper illustrating the structure must be given, any previous code names or designations should be given on first use.

Supplier locations are required for all smaller/local suppliers.

References

Authors are responsible for the accuracy of all references, which must be checked against the original material. Reference citations should be restricted to those that are essential for introducing the purpose and context of the paper, describing methods that are not given in detail, and for discussing the results and any relevant issues raised by them. Authors are responsible for ensuring that references are quoted accurately and not taken out of context. References must not be cited in the synopsis.

Where possible authors should avoid citing conference abstracts or posters (partly because they are not peer reviewed and also because they often report interim findings and the final published studies can often come to substantially different conclusions) and authors MUST NOT cite abstracts that are more than 2 years old without excellent justification for doing so. In addition, abstracts must only be cited if they appear in published abstract books, journal supplements or in a permanent online archive.

References should be cited in the text using sequential numbers. Superscript numbers should be used and should be placed after any punctuation. When referring to several references, separate individual numerals by a comma or a hyphen for a range greater than two references. For instance: This was first discovered by Jones,[1] and later confirmed by several other groups of investigators.[2,3,5-7]

Papers accepted for publication, but not yet published, may be included in the reference list; they should be listed as 'in press', with the name of the journal and the likely year of publication. Submitted work should be quoted as 'unpublished results'. Personal communications and unpublished results, which are permitted in the text only, must include the initials and surnames of all the workers involved; for the former citation, the person's affiliation must be stated, e.g. '(J. Bloggs, NIH, personal communication)', and documentary evidence (an e-mail will suffice) from the person quoted, showing their agreement to be so quoted, must be provided (the agreement must include the exact wording that appears in the paper). All references should be listed numerically at the end of the text. Each reference should be preceded by a number (not superscript) followed by a full stop. Please see the following examples. Failure to conform to Journal style will result in the manuscript being returned to authors.

Examples

Journal reference (<= three authors)
Sanschagrin F, Levesque RC. A specific peptide inhibitor of the class B metallo-B-lactamase L-1 from*Stenotrophomonas maltophilia* identified using phage display. *J Antimicrob Chemother* 2005; **55**: 252-5.

Journal reference (> three authors)
Williams I, Gabriel G, Cohen H *et al*. Zidovudine-the first year of experience. *J Infect* 1989; **18** Suppl 1: 23-31.

Whole book
Long HC, Blatt MA, Higgins MC *et al*. *Medical Decision Making*. Boston: Butterworth-Heinemann, 1997.

Book chapter
Manners T, Jones R, Riley M. Relationship of overweight to haitus hernia and reflux oesophagitis. In: Newman W, ed. *The Obesity Conundrum*. Amsterdam: Elsevier Science, 1997; 352-74.

NCCLS/CLSI methods
National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically—Sixth Edition: Approved Standard M7-A6*. NCCLS, Wayne, PA, USA, 2003.

Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial*

Susceptibility Testing: Fifteenth Informational Supplement M100-S15. CLSI, Wayne, PA, USA, 2005.

Meeting abstract

Hou Y, Qiu Y, Vo NH *et al*. 23-O derivatives of OMT: highly active against *H. influenzae*. In: *Abstracts of the Forty-third Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, 2003*. Abstract F-1187, p. 242. American Society for Microbiology, Washington, DC, USA.

Online material

References to online material should be given in the reference list. Please note that URLs for the suppliers of materials must not be given in either the text or the references. The Journal does not accept any responsibility for the content of web pages cited.

NB – it is no longer necessary to provide the 'date last accessed' for URLs.

Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. Department of Health and Human Services. http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf.

Tables

These should be employed sparingly and should be generally comprehensible without reference to the text. Each table should be supplied on a separate sheet and numbered consecutively using Arabic numerals in the order they are referred to in the text. Each must have a brief descriptive heading. Column headings must clearly explain the content of the column and indicate any units used. Footnotes should be kept to a minimum. Tables must be created using the Table function in Word; they must not be inserted as images. Each data item should occupy a single cell and return characters should not be used within any Table. *JAC* reserves the right to move complicated Tables to online-only Supplementary data.

Figures

These must be employed sparingly to demonstrate important specific points. Figures should be numbered using Arabic numerals in the order in which they are referred to in the text. **In**

figure LEGENDS, symbols should be described in words (e.g. filled circles, open squares etc.). Wherever possible, figures should be two-dimensional. Authors should NOT supply 'three-dimensional' figures unless this is actually necessary to represent the data. The quality of reproduction in *JAC* is limited by the quality of the submitted material. All figures must be of high quality - they should be sharply focused, have good contrast and any lettering must be clear and legible. Colour illustrations can be reproduced if there is sufficient scientific merit in doing so. Authors will be expected to pay for the cost of colour origination in the print version of the Journal (£350/US$600/€525.00 per figure). Alternatively, black and white figures can appear in the printed version of an article with colour versions appearing online (for which there is no charge) – figure legends will need to be suitably worded, e.g. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*. Please state your preferred option (i.e. agreement to pay £350/US$600/€525.00 per figure for print and online colour or preference for online-only colour with no charge) in your covering letter.

Guidance for preparation of Figures

Figures should be sized to fit a single column of the Journal where possible (88 mm) or a double column if necessary (180 mm). The preferred font for lettering is Times; lettering should have an upper case height of 2 mm and a lower case height of 1 mm at publication size (corresponding to point size 8). Line thickness should be set at 0.5 points. Shading used on line drawings should be clear and distinctive; shades of grey and heavy stippling do not reproduce well. Lines and symbols should be drawn boldly enough to withstand reduction. The preferred symbols are filled circles, open circles, filled squares, open squares, filled triangles and open triangles, and should be no smaller than 1 mm (height/diameter) at publication size. Part labels should be lower case letters within parentheses, e.g. (a), (b), (c) etc.

Authors must be ready to supply original gel pictures if requested to do so.

Annex. B.3 Author Guidelines - Journal of Clinical Pharmacy and Therapeutics

1. General

The *Journal of Clinical Pharmacy and Therapeutics (JCPT)* provides a forum for clinicians, pharmacists and pharmacologists to explore and report on issues of common interest. It welcomes five main types of articles

- Editorials
- Original research
- Review articles (including Mini-reviews)
- Commentaries
- Case reports

As our main interest is on novelty, irrespective of the type of contribution, the sub-headings should identify what is known and what is new. A clear description of these aspects is important as they are used by us to filter submissions at the very first stage. This helps us to return manuscripts quickly to authors for submission elsewhere.

Please read the instructions below carefully for details on the submission of manuscripts, the Journal's requirements and standards as well as information concerning the procedure after a manuscript has been accepted for publication in *JCPT*.

2. Ethical Guidelines

JCPT has adopted the following ethical guidelines for publication and research.

2.1 Authorship and Acknowledgements

Authorship: Authors submitting a paper do so on the understanding that the manuscript has been read and approved by all authors and that all authors agree to the submission of the manuscript to the Journal.

JCPT adheres to the definition of authorship set up by The International Committee of Medical Journal Editors (ICMJE). According to the ICMJE authorship criteria, all named authors should meet the following conditions: 1) substantial contributions to conception and design of, or acquisition of data or analysis and interpretation of data, 2) drafting the article or revising it critically for important intellectual content and 3) final approval of the version to

be published. Participation solely in the acquisition of funding or the collection of data does not justify authorship. All people who fulfil the criteria for authorship should be listed as authors. Contributors who do not qualify as authors should be mentioned in Acknowledgements.

The Editors recognise that complex, large-scale and multi-centre research will often result in a significant number of people fulfilling the authorship criteria. However, they reserve the right to ask the lead author to justify the inclusion of more than six authors.

Acknowledgements: Under Acknowledgements please specify contributors to the research/article other than the authors accredited. Please note that research funders are now listed separately under Source of Funding.

2.2 Conflict of Interest and Source of Funding

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Table B.1 Cohen's *d*-value for the difference in the average number of antibiotic prescriptions per patient per year

	Average number of prescription per patient claiming antibiotics during study period						
	2005 (2.22 ± 1.89)	**2006 (2.30 ± 1.97)**	**2007 (2.33 ± 1.95)**	**2008 (2.28 ± 1.91)**	**2009 (2.18 ± 1.75)**	**2010 (2.13 ± 1.74)**	**2011 (2.02 ± 1.63)**
2005 (2.22 ± 1.89)	0.00						
2006 (2.30 ± 1.97)	0.04	0.00					
2007 (2.33 ± 1.95)	0.06	0.02	0.00				
2008 (2.28 ± 1.91)	0.03	0.01	0.03	0.00			
2009 (2.18 ± 1.75)	0.02	0.06	0.08	0.05	0.00		
2010 (2.13 ± 1.74)	0.05	0.09	0.1	0.08	0.03	0.00	
2011 (2.02 ± 1.63)	0.11	0.14	0.16	0.14	0.09	0.06	0.00
2012 (1.98 ± 1.62)	0.13	0.16	0.18	0.16	0.11	0.09	0.03

Table B.2 Cohen's *d*-value for the difference in the average number of antibiotic prescriptions per patient per year stratified by gender

		Average number of prescription per patient claiming antibiotics by gender						
		2005 (2.26 ± 1.90)	**2006 (2.35 ± 2.00)**	**2007 (2.38 ± 1.97)**	**2008 (2.32 ± 1.92)**	**2009 (2.22 ± 1.76)**	**2010 (2.16 ± 1.73)**	**2011 (2.03 ± 1.61)**
Female	**2005 (2.26 ± 1.90)**	0.00						
	2006 (2.35 ± 2.00)	0.05	0.00					
	2007 (2.38 ± 1.97)	0.06	0.02	0.00				
	2008 (2.32 ± 1.92)	0.03	0.02	0.03	0.00			
	2009 (2.22 ± 1.76)	0.02	0.07	0.08	0.05	0.00		
	2010 (2.16 ± 1.73)	0.05	0.10	0.11	0.08	0.03	0.00	
	2011 (2.03 ± 1.61)	0.12	0.16	0.18	0.15	0.11	0.08	0.00
	2012 (1.98 ± 1.58)	0.15	0.19	0.20	0.18	0.14	0.10	0.03
		2005 (2.17 ± 1.86)	**2006 (2.24 ± 1.92)**	**2007 (2.27 ± 1.92)**	**2008 (2.22 ± 1.90)**	**2009 (2.14 ± 1.75)**	**2010 (2.10 ± 1.74)**	**2011 (2.01 ± 1.66)**
Male	**2005 (2.17 ± 1.86)**	0.00						
	2006 (2.24 ± 1.92)	0.04	0.00					
	2007 (2.27 ± 1.92)	0.05	0.02	0.00				
	2008 (2.22 ± 1.90)	0.03	0.01	0.03	0.00			
	2009 (2.14 ± 1.75)	0.02	0.05	0.07	0.04	0.00		
	2010 (2.10 ± 1.74)	0.04	0.07	0.09	0.06	0.02	0.00	
	2011 (2.01 ± 1.66)	0.09	0.12	0.14	0.11	0.07	0.05	0.00
	2012 (1.98 ± 1.66)	0.10	0.14	0.15	0.14	0.09	0.07	0.02

Table B.3 Cohen's *d*-value for the difference in the average number of antibiotic prescriptions per patient per year stratified by age groups

		Average number of prescription per patient claiming antibiotics by age						
		2005	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**
Age (years)		**(2.20 ± 1.76)**	**(2.27 ± 1.82)**	**(2.23 ± 1.81)**	**(2.21 ± 1.76)**	**(2.23 ± 1.72)**	**(2.18 ± 1.69)**	**(2.03 ± 1.53)**
≥0, ≤18	**2005 (2.20 ± 1.76)**	0.00						
	2006 (2.27 ± 1.82)	0.04	0.00					
	2007 (2.23 ± 1.81)	0.02	0.02	0.00				
	2008 (2.21 ± 1.76)	0.01	0.03	0.05	0.00			
	2009 (2.23 ± 1.72)	0.02	0.02	0.04	0.01	0.00		
	2010 (2.18 ± 1.69)	0.01	0.05	0.07	0.02	0.03	0.00	
	2011 (2.03 ± 1.53)	0.10	0.13	0.15	0.10	0.12	0.09	0.00
	2012 (2.00 ± 1.50)	0.11	0.15	0.17	0.12	0.13	0.11	0.02
		(2.02 ± 1.65)	**(2.07 ± 1.69)**	**(2.08 ± 1.65)**	**(2.01 ± 1.57)**	**(1.96 ± 1.49)**	**(1.91 ± 1.44)**	**(1.82 ± 1.36)**
>18, ≤30	**2005 (2.02 ± 1.65)**	0.00						
	2006 (2.07 ± 1.69)	0.03	0.00					
	2007 (2.08 ± 1.65)	0.03	0.06	0.00				
	2008 (2.01 ± 1.57)	0.01	0.04	0.04	0.00			
	2009 (1.96 ± 1.49)	0.04	0.07	0.07	0.03	0.00		
	2010 (1.91 ± 1.44)	0.07	0.09	0.10	0.06	0.03	0.00	
	2011 (1.82 ± 1.36)	0.12	0.15	0.16	0.12	0.09	0.06	0.00
	2012 (1.80 ± 1.34)	0.13	0.16	0.17	0.13	0.11	0.08	0.01

Table B.3 Cohen's *d*-value for the difference in the average number of antibiotic prescriptions per patient per year stratified by age groups (continued)

		Average number of prescription per patient claiming antibiotics by age						
Age (years)		**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**
		(2.41 ± 2.15)	**(2.52 ± 2.27)**	**(2.56 ± 2.23)**	**(2.49 ± 2.19)**	**(2.27 ± 1.88)**	**(2.21 ± 1.88)**	**(2.10 ± 1.79)**
>30, ≤45	**2005 (2.41 ± 2.15)**	0.00						
	2006 (2.52 ± 2.27)	0.05	0.00					
	2007 (2.56 ± 2.23)	0.07	0.02	0.00				
	2008 (2.49 ± 2.19)	0.04	0.01	0.03	0.00			
	2009 (2.27 ± 1.88)	0.07	0.11	0.13	0.10	0.00		
	2010 (2.21 ± 1.88)	0.09	0.14	0.16	0.13	0.03	0.00	
	2011 (2.10 ± 1.79)	0.14	0.19	0.21	0.18	0.09	0.06	0.00
	2012 (2.06 ± 1.80)	0.16	0.20	0.09	0.20	0.11	0.08	0.02
		(2.25 ± 1.94)	**(2.35 ± 2.03)**	**(2.39 ± 2.04)**	**(2.38 ± 2.01)**	**(2.25 ± 1.85)**	**(2.19 ± 1.93)**	**(2.11 ± 1.76)**
>45, ≤65	**2005 (2.25 ± 1.94)**	0.00						
	2006 (2.35 ± 2.03)	0.05	0.00					
	2007 (2.39 ± 2.04)	0.07	0.02	0.00				
	2008 (2.38 ± 2.01)	0.05	0.01	0.01	0.00			
	2009 (2.25 ± 1.85)	0.00	0.05	0.07	0.04	0.00		
	2010 (2.19 ± 1.93)	0.03	0.08	0.10	0.08	0.03	0.00	
	2011 (2.11 ± 1.76)	0.07	0.12	0.14	0.12	0.08	0.04	0.00
	2012 (2.08 ± 1.77)	0.09	0.13	0.15	0.14	0.09	0.06	0.02

Table B.3 Cohen's *d*-value for the difference in the average number of antibiotic prescriptions per patient per year stratified by age groups (continued)

		Average number of prescription per patient claiming antibiotics by age						
Age (years)		**2005 (1.97 ± 1.54)**	**2006 (2.10 ± 1.57)**	**2007 (2.04 ± 1.60)**	**2008 (2.04 ± 1.62)**	**2009 (2.03 ± 1.60)**	**2010 (2.04 ± 1.63)**	**2011 (1.92 ± 1.50)**
>65	**2005 (1.97 ± 1.54)**	0.00						
	2006 (2.10 ± 1.57)	0.03	0.00					
	2007 (2.04 ± 1.60)	0.04	0.02	0.00				
	2008 (2.04 ± 1.62)	0.04	0.02	0.00	0.00			
	2009 (2.03 ± 1.60)	0.04	0.01	0.01	0.01	0.00		
	2010 (2.04 ± 1.63)	0.04	0.02	0.00	0.00	0.01	0.00	
	2011 (1.92 ± 1.50)	0.03	0.06	0.08	0.07	0.11	0.07	0.00
	2012 (1.81 ± 1.37)	0.10	0.13	0.14	0.14	0.14	0.14	0.07

Table B.4 Cohen's *d*-value for the difference in the average number of antibiotic prescriptions per patient per year stratified by provinces

Province		Average number of prescription per patient claiming antibiotics by province, (Average ± SD)						
		2005 (2.05 ± 1.74)	**2006 (2.18 ± 1.85)**	**2007 (2.25 ± 1.81)**	**2008 (2.27 ± 1.86)**	**2009 (2.18 ± 1.75)**	**2010 (2.12 ± 1.73)**	**2011 (2.07 ± 1.73)**
Eastern Cape	**2005 (2.05 ± 1.74)**	0.00						
	2006 (2.18 ± 1.85)	0.07	0.00					
	2007 (2.25 ± 1.81)	0.11	0.04	0.00				
	2008 (2.27 ± 1.86)	0.11	0.05	0.01	0.00			
	2009 (2.18 ± 1.75)	0.07	0.00	0.04	0.05	0.00		
	2010 (2.12 ± 1.73)	0.04	0.03	0.07	0.08	0.03	0.00	
	2011 (2.07 ± 1.73)	0.01	0.06	0.10	0.11	0.06	0.03	0.00
	2012 (2.06 ± 1.62)	0.01	0.06	0.10	0.11	0.07	0.03	0.01
		2005 (2.05 ± 1.64)	**2006 (2.16 ± 1.73)**	**2007 (2.21 ± 1.73)**	**2008 (2.17 ± 1.77)**	**2009 (2.10 ± 1.70)**	**2010 (2.12 ± 1.73)**	**2011 (2.02 ± 1.63**
Free State	**2005 (2.05 ± 1.64)**	0.00						
	2006 (2.16 ± 1.73)	0.06	0.00					
	2007 (2.21 ± 1.73)	0.09	0.03	0.00				
	2008 (2.17 ± 1.77)	0.07	0.01	0.02	0.00			
	2009 (2.10 ± 1.70)	0.03	0.03	0.06	0.04	0.00		
	2010 (2.12 ± 1.73)	0.04	0.02	0.05	0.03	0.01	0.00	
	2011 (2.02 ± 1.63)	0.02	0.08	0.11	0.08	0.05	0.06	0.00
	2012 (1.96 ± 1.62)	0.06	0.12	0.14	0.12	0.08	0.09	0.04
		2005 (2.24 ± 1.89)	**2006 (2.35 ± 1.99)**	**2007 (2.36 ± 1.97)**	**2008 (2.30 ± 1.89)**	**2009 (2.20 ± 1.70)**	**2010 (2.14 ± 1.68)**	**2011 (2.00 ± 1.63)**
Gauteng	**2005 (2.24 ± 1.89)**	0.00						
	2006 (2.35 ± 1.99)	0.06	0.00					
	2007 (2.36 ± 1.97)	0.06	0.01	0.00				
	2008 (2.30 ± 1.89)	0.03	0.03	0.03	0.00			
	2009 (2.20 ± 1.70)	0.02	0.08	0.08	0.05	0.00		
	2010 (2.14 ± 1.68)	0.05	0.11	0.11	0.08	0.03	0.00	
	2011 (2.00 ± 1.63)	0.13	0.18	0.18	0.19	0.12	0.08	0.00
	2012 (1.96 ± 1.52)	0.15	0.20	0.20	0.18	0.14	0.11	0.02

Table B.4 Cohen's *d*-value for the difference in the average number of antibiotic prescriptions per patient per year stratified by provinces (continued)

Province		Average number of prescription per patient claiming antibiotics by province, (Average ± SD)						
		2005 (2.49 ± 2.26)	2006 (2.55 ± 2.35)	2007 (2.55 ± 2.30)	2008 (2.42 ± 2.12)	2009 (2.28 ± 1.89)	2010 (2.23 ± 1.91)	2011 (2.08 ± 1.73)
Kwazulu-Natal	**2005 (2.49 ± 2.26)**	0.00						
	2006 (2.55 ± 2.35)	0.03	0.00					
	2007 (2.55 ± 2.30)	0.03	0.00	0.00				
	2008 (2.42 ± 2.12)	0.03	0.06	0.06	0.00			
	2009 (2.28 ± 1.89)	0.09	0.11	0.11	0.07	0.00		
	2010 (2.23 ± 1.91)	0.12	0.14	0.14	0.09	0.03	0.00	
	2011 (2.08 ± 1.73)	0.18	0.20	0.20	0.16	0.11	0.08	0.00
	2012 (2.04 ± 1.68)	0.20	0.22	0.22	0.18	0.13	0.10	0.02
		2005 (2.30 ± 1.94)	**2006 (2.38 ± 2.00)**	**2007 (2.31 ± 1.92)**	**2008 (2.25 ± 1.87)**	**2009 (2.09 ± 1.65)**	**2010 (2.04 ± 1.65)**	**2011 (1.94 ± 1.60)**
Limpopo	**2005 (2.30 ± 1.94)**	0.00						
	2006 (2.38 ± 2.00)	0.04	0.00					
	2007 (2.31 ± 1.92)	0.01	0.04	0.00				
	2008 (2.25 ± 1.87)	0.03	0.07	0.03	0.00			
	2009 (2.09 ± 1.65)	0.11	0.15	0.11	0.09	0.00		
	2010 (2.04 ± 1.65)	0.13	0.17	0.14	0.11	0.03	0.00	
	2011 (1.94 ± 1.60)	0.19	0.22	0.19	0.17	0.09	0.06	0.00
	2012 (1.94 ± 1.63)	0.19	0.22	0.19	0.17	0.09	0.06	0.00
		2005 (2.30 ± 1.91)	**2006 (2.27 ± 1.85)**	**2007 (2.40 ± 1.97)**	**2008 (2.37 ± 2.05)**	**2009 (2.28 ± 1.88)**	**2010 (2.24 ± 1.89)**	**2011 (2.18 ± 1.85)**
Mpumalanga	**2005 (2.30 ± 1.91)**	0.00						
	2006 (2.27 ± 1.85)	0.02	0.00					
	2007 (2.40 ± 1.97)	0.05	0.08	0.00				
	2008 (2.37 ± 2.05)	0.03	0.03	0.01	0.00			
	2009 (2.28 ± 1.88)	0.10	0.01	0.06	0.04	0.00		
	2010 (2.24 ± 1.89)	0.03	0.02	0.08	0.06	0.02	0.00	
	2011 (2.18 ± 1.85)	0.06	0.05	0.11	0.09	0.05	0.03	0.00
	2012 (2.13 ± 1.84)	0.09	0.08	0.14	0.11	0.08	0.06	0.03

Table B.4 Cohen's *d*-value for the difference in the average number of antibiotic prescriptions per patient per year stratified by provinces (continued)

Province		Average number of prescription per patient claiming antibiotics by province, (Average ± SD)						
		2005 (2.14 ± 1.71)	**2006 (2.31 ± 1.82)**	**2007 (2.29 ± 1.77)**	**2008 (2.32 ± 2.02)**	**2009 (2.10 ± 1.64)**	**2010 (2.04 ± 1.58)**	**2011 (1.95 ± 1.53)**
North-West	**2005 (2.14 ± 1.71)**	0.00						
	2006 (2.31 ± 1.82)	0.09	0.00					
	2007 (2.29 ± 1.77)	0.08	0.01	0.00				
	2008 (2.32 ± 2.02)	0.09	0.01	0.01	0.00			
	2009 (2.10 ± 1.64)	0.02	0.12	0.11	0.11	0.00		
	2010 (2.04 ± 1.58)	0.06	0.15	0.14	0.14	0.04	0.00	
	2011 (1.95 ± 1.53)	0.11	0.20	0.24	0.18	0.09	0.06	0.00
	2012 (1.94 ± 1.60)	0.12	0.20	0.20	0.19	0.10	0.06	0.01
		2005 (1.89 ± 1.45)	**2006 (1.99 ± 1.55)**	**2007 (2.08 ± 1.58)**	**2008 (2.09 ± 1.69)**	**2009 (2.04 ± 1.62)**	**2010 (2.01 ± 1.59)**	**2011 (1.98 ± 1.58)**
Northern Cape	**2005 (1.89 ± 1.45)**	0.00						
	2006 (1.99 ± 1.55)	0.06	0.00					
	2007 (2.08 ± 1.58)	0.12	0.06	0.00				
	2008 (2.09 ± 1.69)	0.12	0.06	0.01	0.00			
	2009 (2.04 ± 1.62)	0.09	0.03	0.02	0.03	0.00		
	2010 (2.01 ± 1.59)	0.08	0.01	0.04	0.05	0.02	0.00	
	2011 (1.98 ± 1.58)	0.06	0.01	0.06	0.07	0.04	0.02	0.00
	2012 (1.89 ± 1.55)	0.00	0.06	0.12	0.12	0.09	0.08	0.06
		2005 (1.96 ± 1.52)	**2006 (1.97 ± 1.54)**	**2007 (2.02 ± 1.56)**	**2008 (1.98 ± 1.54)**	**2009 (2.10 ± 1.84)**	**2010 (2.07 ± 1.82)**	**2011 (2.00 ± 1.76)**
Western Cape	**2005 (1.96 ± 1.52)**	0.00						
	2006 (1.97 ± 1.54)	0.01	0.00					
	2007 (2.02 ± 1.56)	0.04	0.03	0.00				
	2008 (1.98 ± 1.54)	0.01	0.01	0.03	0.00			
	2009 (2.10 ± 1.84)	0.08	0.07	0.04	0.07	0.00		
	2010 (2.07 ± 1.82)	0.06	0.05	0.03	0.05	0.02	0.00	
	2011 (2.00 ± 1.76)	0.02	0.01	0.01	0.01	0.05	0.04	0.00
	2012 (1.97 ± 1.73)	0.01	0.00	0.03	0.01	0.07	0.05	0.03

Table B.5 Cohen's *d*-value for the difference in the average number of antibiotic prescriptions per patient per year according to age groups stratified by the study period

Study period	Age (years)	Average number of prescription per patient claimed by age, Average ± SD				
			≥0, ≤18 (2.20 ± 1.76)	**>18, ≤30 (2.02 ± 1.65)**	**>30, ≤45 (2.41 ± 2.15)**	**>45, ≤65 (2.25 ± 1.94)**
2005	**≥0, ≤18**	(2.20 ± 1.76)	0.00			
	>18, ≤30	(2.02 ± 1.65)	0.10	0.00		
	>30, ≤45	(2.41 ± 2.15)	0.10	0.18	0.00	
	>45, ≤65	(2.25 ± 1.94)	0.03	0.12	0.07	0.00
	> 65	(1.97 ± 1.54)	0.13	0.03	0.20	0.14
			≥0, ≤18 (2.27 ± 1.82)	**>18, ≤30 (2.07 ± 1.69)**	**>30, ≤45 (2.52 ± 2.27)**	**>45, ≤65 (2.35 ± 2.03)**
2006	**≥0, ≤18**	(2.27 ± 1.82)	0.00	0.00		
	>18, ≤30	(2.07 ± 1.69)	0.11	0.00		
	>30, ≤45	(2.52 ± 2.27)	0.11	0.20	0.00	
	>45, ≤65	(2.35 ± 2.03)	0.04	0.14	0.07	0.00
	> 65	(2.10 ± 1.57)	0.09	0.02	0.19	0.12
			≥0, ≤18 (2.23 ± 1.81)	**>18, ≤30 (2.08 ± 1.65)**	**>30, ≤45 (2.56 ± 2.23)**	**>45, ≤65 (2.39 ± 2.04)**
2007	**≥0, ≤18**	(2.23 ± 1.81)	0.00			
	>18, ≤30	(2.08 ± 1.65)	0.08	0.00		
	>30, ≤45	(2.56 ± 2.23)	0.15	0.22	0.00	
	>45, ≤65	(2.39 ± 2.04)	0.08	0.15	0.08	0.00
	> 65	(2.04 ± 1.60)	0.10	0.02	0.23	0.17
			≥0, ≤18 (2.21 ± 1.76)	**>18, ≤30 (2.01 ± 1.57)**	**>30, ≤45 (2.49 ± 2.19)**	**>45, ≤65 (2.38 ± 2.01)**
2008	**≥0, ≤18**	(2.21 ± 1.76)	0.00			
	>18, ≤30	(2.01 ± 1.57)	0.11	0.00		
	>30, ≤45	(2.49 ± 2.19)	0.13	0.22	0.00	
	>45, ≤65	(2.38 ± 2.01)	0.08	0.18	0.05	0.00
	> 65	(2.04 ± 1.62)	0.17	0.02	0.21	0.17
			≥0, ≤18 (2.23 ± 1.72)	**>18, ≤30 (1.96 ± 1.49)**	**>30, ≤45 (2.27 ± 1.88)**	**>45, ≤65 (2.25 ± 1.85)**
2009	**≥0, ≤18**	(2.23 ± 1.72)	0.00			
	>18, ≤30	(1.96 ± 1.49)	0.16	0.00		
	>30, ≤45	(2.27 ± 1.88)	0.02	0.16	0.00	
	>45, ≤65	(2.25 ± 1.85)	0.01	0.16	0.01	0.00
	> 65	(2.03 ± 1.60)	0.12	0.04	0.13	0.12

Table B.5 Cohen's *d*-value for the difference in the average number of antibiotic prescriptions per patient per year according to age groups stratified by the study period (continued)

Study period	Age (years)	Average number of prescription per patient claimed by age, Average ± SD				
			≥0, ≤18 (2.18 ± 1.69)	**>18, ≤30 (1.91 ± 1.44)**	**>30, ≤45 (2.21 ± 1.88)**	**>45, ≤65 (2.19 ± 1.93)**
2010	**≥0, ≤18**	(2.18 ± 1.69)	0.00			
	>18, ≤30	(1.91 ± 1.44)	0.16	0.00		
	>30, ≤45	(2.21 ± 1.88)	0.02	0.16	0.00	
	>45, ≤65	(2.19 ± 1.93)	0.01	0.15	0.01	0.00
	> 65	(2.04 ± 1.63)	0.08	0.08	0.09	0.08
			≥0, ≤18 (2.03 ± 1.53)	**>18, ≤30 (1.82 ± 1.36)**	**>30, ≤45 (2.10 ± 1.79)**	**>45, ≤65 (2.11 ± 1.76)**
2011	**≥0, ≤18**	(2.03 ± 1.53)	0.00			
	>18, ≤30	(1.82 ± 1.36)	0.14	0.00		
	>30, ≤45	(2.10 ± 1.79)	0.04	0.16	0.00	
	>45, ≤65	(2.11 ± 1.76)	0.05	0.16	0.01	0.00
	> 65	(1.92 ± 1.50)	0.07	0.07	0.10	0.11
			≥0, ≤18 (2.00 ± 1.50)	**>18, ≤30 (1.80 ± 1.34)**	**>30, ≤45 (2.06 ± 1.80)**	**>45, ≤65 (2.08 ± 1.77)**
2012	**≥0, ≤18**	(2.00 ± 1.50)	0.00			
	>18, ≤30	(1.80 ± 1.34)	0.13	0.00		
	>30, ≤45	(2.06 ± 1.80)	0.03	0.14	0.00	
	>45, ≤65	(2.08 ± 1.77)	0.05	0.16	0.01	0.00
	> 65	(1.81 ± 1.37)	0.13	0.01	0.14	0.15

Table B.6 Cohen's *d*-value for the difference in the average number of antibiotic agents claimed during study period

	Average number of medicine items claimed during study period						
	2005 (1.05 ± 0.19)	**2006 (1.05 ± 0.19)**	**2007 (1.05 ± 0.19)**	**2008 (1.05 ± 0.20)**	**2009 (1.05 ± 0.20)**	**2010 (1.05 ± 0.19)**	**2011 (1.05 ± 0.20)**
2005 (1.05 ± 0.19)	0.00						
2006 (1.05 ± 0.19)	0.00	0.00					
2007 (1.05 ± 0.19)	0.00	0.00	0.00				
2008 (1.05 ± 0.20)	0.00	0.00	0.00	0.00			
2009 (1.05 ± 0.20)	0.00	0.00	0.00	0.00	0.00		
2010 (1.05 ± 0.19)	0.00	0.00	0.00	0.00	0.00	0.00	
2011 (1.05 ± 0.20)	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2012 (1.06 ± 0.21)	0.05	0.05	0.05	0.05	0.05	0.05	0.05

Table B.7 Cohen's *d*-value for the difference in the average number of antibiotic agents claimed per year stratified by gender

		2005 (1.06 ± 0.20)	**2006 (1.05 ± 0.20)**	**2007 (1.02 ± 0.15)**	**2008 (1.06 ± 0.21)**	**2009 (1.06 ± 0.21)**	**2010 (1.06 ± 0.20)**	**2011 (1.06 ± 0.21)**
Female	**2005 (1.06 ± 0.20)**	0.00						
	2006 (1.05 ± 0.20)	0.05	0.00					
	2007 (1.02 ± 0.15)	0.20	0.15	0.00				
	2008 (1.06 ± 0.21)	0.00	0.05	0.19	0.00			
	2009 (1.06 ± 0.21)	0.00	0.05	0.19	0.00	0.00		
	2010 (1.06 ± 0.20)	0.00	0.05	0.20	0.00	0.00	0.00	
	2011 (1.06 ± 0.21)	0.00	0.05	0.19	0.00	0.00	0.00	0.00
	2012 (1.06 ± 0.22)	0.00	0.05	0.18	0.00	0.00	0.00	0.00
		2005 (1.05 ± 0.19)	**2006 (1.05 ± 0.19)**	**2007 (1.05 ± 0.19)**	**2008 (1.06 ± 0.20)**	**2009 (1.05 ± 0.20)**	**2010 (1.05 ± 0.20)**	**2011 (1.05 ± 0.20)**
Male	**2005 (1.05 ± 0.19)**	0.00						
	2006 (1.05 ± 0.19)	0.00	0.00					
	2007 (1.05 ± 0.19)	0.00	0.00	0.00				
	2008 (1.06 ± 0.20)	0.05	0.05	0.06	0.00			
	2009 (1.05 ± 0.20)	0.00	0.00	0.00	0.05	0.00		
	2010 (1.05 ± 0.20)	0.00	0.00	0.00	0.05	0.00	0.00	
	2011 (1.05 ± 0.20)	0.00	0.00	0.00	0.05	0.00	0.00	0.00
	2012 (1.06 ± 0.21)	0.05	0.05	0.05	0.00	0.05	0.05	0.05

Table B.8 Cohen's *d*-value for the difference in the average number of antibiotic agents claimed per year stratified by age groups

		Average number antibiotic agents items claimed age groups						Average number antibiotic agents items claimed age groups			
Study period		**≥0, ≤18 (1.04 ± 0.17)**	**>18, ≤30 (1.06 ± 0.21)**	**>30, ≤45 (1.07 ± 0.21)**	**>45, ≤65 (1.06 ± 0.20)**	**Study Period**		**≥0, ≤18 (1.04 ± 0.17)**	**>18, ≤30 (1.05 ± 0.21)**	**>30, ≤45 (1.07 ± 0.21)**	**>45, ≤65 (1.05 ± 0.19)**
2005	**≥0, ≤18 (1.04 ± 0.17)**	0.00				**2006**	**≥0, ≤18 (1.04 ± 0.17)**	0.00			
	>18, ≤30 (1.06 ± 0.21)	0.10					**>18, ≤30 (1.05 ± 0.21)**	0.09			
	>30, ≤45 (1.07 ± 0.21)	0.15	0.06				**>30, ≤45 (1.07 ± 0.21)**	0.16	0.06		
	>45, ≤65 (1.06 ± 0.20)	0.08	0.02	0.08			**>45, ≤65 (1.05 ± 0.19)**	0.08	0.01	0.07	
	> 65 (1.02 ± 0.14)	0.08	0.17	0.23	0.15		**> 65 (1.03 ± 0.14)**	0.07	0.16	0.22	0.15
		≥0, ≤18 (1.04 ± 0.17)	**>18, ≤30 (1.06 ± 0.21)**	**>30, ≤45 (1.07 ± 0.21)**	**>45, ≤65 (1.06 ± 0.19)**			**≥0, ≤18 (1.04 ± 0.18)**	**>18, ≤30 (1.06 ± 0.22)**	**>30, ≤45 (1.07 ± 0.22)**	**>45, ≤65 (1.06 ± 0.20)**
2007	**≥0, ≤18 (1.04 ± 0.17)**	0.00				**2008**	**≥0, ≤18 (1.04 ± 0.18)**	0.00			
	>18, ≤30 (1.06 ± 0.21)	0.10					**>18, ≤30 (1.06 ± 0.22)**	0.09			
	>30, ≤45 (1.07 ± 0.21)	0.15	0.05				**>30, ≤45 (1.07 ± 0.22)**	0.14	0.05		
	>45, ≤65 (1.06 ± 0.19)	0.09	0.00	0.06			**>45, ≤65 (1.06 ± 0.20)**	0.09	0.00	0.05	
	> 65 (1.02± 0.14)	0.07	0.17	0.22	0.16		**> 65 (1.03 ± 0.15)**	0.07	0.16	0.21	0.16

Table B.8 Cohen's *d*-value for the difference in the average number of antibiotic agents claimed per year stratified by age groups (continued)

		Average number of antibiotic agents claimed by age groups						Average number of antibiotic agents claimed by age groups			
Study period		**≥0, ≤18 (1.04 ± 0.19)**	**>18, ≤30 (1.06 ± 0.22)**	**>30, ≤45 (1.07 ± 0.22)**	**>45, ≤65 (1.06 ± 0.21)**	**Study period**		**≥0, ≤18 (1.04 ± 0.18)**	**>18, ≤30 (1.06 ± 0.22)**	**>30, ≤45 (1.07 ± 0.22)**	**>45, ≤65 (1.06 ± 0.20)**
2009	**≥0, ≤18 (1.04 ± 0.19)**	0.00				**2010**	**≥0, ≤18 (1.04 ± 0.18)**	0.00			
	>18, ≤30 (1.06 ± 0.22)	0.09					**>18, ≤30 (1.06 ± 0.22)**	0.1	0.00		
	>30, ≤45 (1.07 ± 0.22)	0.12	0.03				**>30, ≤45 (1.07 ± 0.22)**	0.12	0.02		
	>45, ≤65 (1.06 ± 0.21)	0.07	0.01	0.04			**>45, ≤65 (1.06 ± 0.20)**	0.09	0.00	0.03	
	> 65 (1.03 ± 0.15)	0.06	0.15	0.18	0.14		**> 65 (1.03 ± 0.15)**	0.05	0.15	0.17	0.13
		≥0, ≤18 (1.04 ± 0.18)	**>18, ≤30 (1.06 ± 0.22)**	**>30, ≤45 (1.07 ± 0.22)**	**>45, ≤65 (1.06 ± 0.21)**			**≥0, ≤18 (1.05 ± 0.19)**	**>18, ≤30 (1.07 ± 0.23)**	**>30, ≤45 (1.07 ± 0.24)**	**>45, ≤65 (1.07± 0.22)**
2011	**≥0, ≤18 (1.04 ± 0.18)**	0.00				**2012**	**≥0, ≤18 (1.05 ± 0.19)**	0.00			
	>18, ≤30 (1.06 ± 0.22)	0.1					**>18, ≤30 (1.07 ± 0.23)**	0.10			
	>30, ≤45 (1.07 ± 0.22)	0.12	0.02				**>30, ≤45 (1.07 ± 0.24)**	0.12	0.03		
	>45, ≤65 (1.06 ± 0.21)	0.09	0.02	0.04			**>45, ≤65 (1.07± 0.22)**	0.10	0.00	0.03	
	> 65 (1.03 ± 0.15)	0.05	0.16	0.18	0.14		**> 65 (1.03 ± 0.16)**	0.06	0.15	0.18	0.15

Table B.9 Number of antibiotic prescriptions per patient per year according to seasonal trends

	2005 (N = 1 174 679)			2006 (N = 1 220 991)			2007 (N = 1 022 803)		
	Season 1	**Season 2**	**Season 3**	**Season 1**	**Season 2**	**Season 3**	**Season 1**	**Season 2**	**Season 3**
Female	203 679 (30.9)	259 410 (39.4)	196 045 (29.7)	226 399 (33.0)	273 135 (39.8)	187 481 (27.3)	199 279 (34.5)	224 328 (38.8)	153 937 (26.7)
Male	159 323 (31.0)	205 550 (40.0)	149 089 (29.0)	174 511 (32.7)	214 309 (40.2)	144 324 (27.1)	152 137 (34.2)	175 129 (39.4)	117 765 (28.5)
Unidentified	496 (29.7)	653 (29.0)	434 (29.4)	378 (45.4)	290 (34.9)	164 (19.7)	109 (47.8)	119 (52.19)	0 (0.0)
Age									
>0, ≤18	109 207 (31.2)	140 089 (40.0)	100 761 (28.8)	118 180 (33.3)	141 983 (40.1)	94 318 (26.6)	100 763 (35.6)	110 103 (38.8)	72 582 (25.6)
>18, ≤30	48 137 (32.0)	58 221 (38.7)	44 189 (29.4)	54 025 (33.3)	64 463 (39.7)	43 897 (27.0)	48 867 (35.6)	54 104 (39.5)	34 164 (24.9)
>30, ≤45	96 882 (31.3)	120 206 (38.8)	92 722 (30.0)	104 894 (33.2)	124 660 (39.4)	86 685 (27.4)	88 679 (34.9)	98 096 (38.6)	67 188 (26.5)
>45, ≤65	82 681 (30.2)	110 131 (40.2)	81 296 (29.7)	95 467 (32.3)	119 074 (40.3)	81 001 (27.4)	86 404 (32.8)	103 690 (39.4)	73 021 (27 8)
> 65	26 591 (7.3)	36 966 (41.0)	26 600 (29.5)	28 722 (31.1)	37 554 (40.7)	26 068 (28.2)	26 812 (31.5)	33 583 (39.4)	24 747 (29.1)
Provinces									
Eastern Cape	21 734 (26.7)	35 434 (43.5)	24 231 (29.8)	25 145 (32.5)	31 553 (40.8)	20 584 (26.6)	21 646 (34.2)	24 429 (38.7)	17 095 (27.1)
Free State	14 256 (29.3)	20 433 (41.9)	14 036 (28.8)	16 296 (31.0)	22 297 (42.4)	13 995 (26.6)	14 054 (33.5)	16 985 (40.4)	10 980 (26.1)
Gauteng	145 547 (31.4)	183 872 (39.6)	134 734 (29.0)	163 976 (32.5)	204 321 (40.5)	136 509 (27.0)	141 967 (33.7)	168 770 (40.0)	111 202 (26.4)
Kwazulu-Natal	60 003 (32.4)	71 839 (38.8)	53 465 (28.9)	62 038 (33.6)	72 577 (39.3)	50 254 (27.2)	57 998 (36.0)	59 489 (36.9)	43 603 (27.1)
Limpopo	31 767 (33.6)	35 232 (37.2)	27 657 (29.2)	34 317 (34.7)	37 966 (38.4)	26 728 (27.0)	28 700 (36.8)	28 852 (37.0)	20 516 (26.3)
Mpumalanga	24 003 (32.9)	28 117 (38.5)	20 838 (28.6)	27 042 (32.2)	33 397 (39.8)	23 500 (28.0)	25 452 (35.3)	27 612 (38.3)	19 031 (26.4)
North-West	22 311 (30.1)	27 444 (37.0)	24 340 (32.9)	29 722 (33.7)	34 906 (39.6)	23 608 (26.8)	25 992 (34.8)	29 342 (39.3)	19 329 (25.9)
Northern Cape	4 895 (26.3)	7 434 (40.0)	6 322 (33.9)	5 941 (51.7)	7 809 (41.7)	4 983 (26.6)	4 984 (32.2)	6 322 (40.8)	4 175 (27.0)
Western Cape	31 336 (29.6)	43 374 (40.9)	31 296 (29.5)	31 962 (30.7)	41 355 (39.7)	30 857 (29.6)	29 373 (32.3)	36 440 (40.1)	25 042 (27.6)
Not indicated	7 646 (26.6)	12 434 (43.3)	8 649 (30.1)	4 849 (65.95)	1 553 (21.1)	951 (12.9)	1 359 (39.7)	1 335 (39.0)	729 (21.3)

Table B.9 Number of antibiotic prescriptions per patient per years according to seasonal trends (continued)

	2008 (N = 808 310)			2009 (N = 1 060 275)			2010 (N = 940 992)		
	Season 1	**Season 2**	**Season 3**	**Season 1**	**Season 2**	**Season 3**	**Season 1**	**Season 2**	**Season 3**
Female	166 911 (36.6)	173 352 (38.0)	115 907 (25.4)	200 599 (34.1)	231 772 (39.4)	155 796 (26.5)	175 609 (33.8)	202 006 (38.9)	141 492 (27.3)
Male	128 784 (36.6)	135 334 (38.4)	88 022 (25.0)	158 378 (33.6)	188 816 (40.0)	124 914 (26.5)	140 404 (33.3)	165 759 (39.3)	115 722 (27.4)
Age									
≥0, ≤18	74 513 (37.8)	75 522 (38.28)	47 272 (24.0)	95 475 (33.9)	115 024 (40.9)	70 772 (25.2)	82 478 (34.2)	93 404 (38.7)	65 210 (27.1)
>18, ≤30	40 300 (38.6)	39 690 (38.0)	24 343 (23.3)	53 792 (34.1)	63 762 (40.4)	40 322 (25.5)	46 929 (33.5)	55 879 (39.9)	37 221 (26.6)
>30, ≤45	71 810 (37.3)	73 274 (38.0)	47 652 (24.70	84 022 (34.5)	94 742 (38.9)	64 550 (26.5)	72 350 (33.7)	83 344 (38.8)	59 036 (27.5)
>45, ≤65	83 005 (35.2)	91 125 (38.6)	61 964 (26.3)	93 137 (33.5)	109 080 (39.2)	75 819 (27.3)	83 080 (33.5)	97 293 (39.2)	67 732 (27.3)
> 65	26 067 (33.5)	29 075 (37.4)	22 698 (29.2)	32 551 (32.6)	37 980 (38.1)	29 247 (29.3)	31 176 (32.1)	37 845 (39.0)	28 015 (28.9)
Province									
Eastern Cape	19 432 (36.9)	19 993 (37.9)	13 278 (25.2)	22 534 (33.6)	26 206 (39.1)	18 343 (27.4)	19 900 (33.8)	22 207 (37.7)	16 812 (28.5)
Free State	12 180 (35.2)	13 766 (39.8)	8 627 (25.0)	14 917 (32.1)	18 735 (40.4)	12 757 (27.5)	14 467 (32.5)	17 860 (40.1)	12 233 (27.5)
Gauteng	122 279 (36.1)	130 653 (38.5)	86 271 (25.4)	157 537 (33.6)	188 230 (40.2)	122 631 (26.2)	139 184 (33.4)	167 164 (40.1)	110 889 (26.6)
Kwazulu-Natal	48 662 (37.9)	48 320 (37.6)	31 502 (24.5)	55 399 (35.8)	59 039 (38.2)	40 179 (26.0)	45 628 (35.7)	46 706 (36.6)	35 444 (27.7)
Limpopo	21 630 (38.2)	21 051 (37.2)	13 929 (25.6)	19 297 (36.4)	20 222 (38.1)	13 545 (25.5)	15 007 (34.6)	16 691 (38.4)	11 737 (27.0)
Mpumalanga	20 596 (36.6)	21 289 (37.8)	14 393 (25.6)	25 083 (33.6)	29 455 (39.4)	20 206 (27.0)	23 086 (32.9)	26 973 (38.5)	20 056 (28.6
North-West	20 822 (37.7)	20 914 (37.9)	13 524 (24.5)	23 495 (33.2)	28 460 (40.2)	18 854 (26.6)	21 701 (33.2)	26 052 (40.0)	17 567 (26.9)
Northern Cape	4 154 (35.1)	4 578 (38.7)	3 099 (26.19)	4 704 (31.7)	6 010 (40.5)	4 118 (27.8)	4 743 (30.78)	6 276 (40.7)	4 388 (28.5)
Western Cape	25 041 (35.2)	27 293 (38.3)	18 886 (26.5)	34 187 (32.4)	42 333 (40.2)	28 876 (27.4)	30 366 (32.6)	35 981 (38.6)	26 940 (28.9)
Not indicated	899 (41.9)	829 (38.6)	420 (19.6)	1 824 (37.1)	1 898 (38.6)	1 201 (24.4)	1 931 (39.1)	1 855 (37.6)	1 148 (23.3)

Table B.9 Number of antibiotic prescriptions per patient per years according to seasonal trends (continued)

	2011 (N = 768 963)			2012 (N = 678 165)		
	Season 1	**Season 2**	**Season 3**	**Season 1**	**Season 2**	**Season 3**
Female	152 143 (36.5)	159 318 (38.2)	105 390 (25.3)	128 985 (35.9)	140 456 (39.1)	89 611 (25.0)
Male	126 122 (35.8)	135 471 (38.5)	90 516 (25.7)	111 241 (34.9)	126 628 (39.7)	81 238 (25.5)
Age						
≥0, ≤18	71 806 (37.1)	72 369 (37.4)	49 505 (25.6)	60 838 (35.4)	68 755 (40.0)	42 178 (24.6)
>18, ≤30	41 071 (36.7)	43 019 (38.4)	27 810 (24.9)	34 282 (35.3)	38 201 (39.3)	24 681 (25.4)
>30, ≤45	64 071 (35.7)	68 854 (38.4)	46 396 (25.9)	55 659 (34.8)	63 023 (39.4)	41 284 (25.8)
>45, ≤65	72 200 (35.5)	79 434 (39.0)	51 865 (25.5)	62 813 (34.4)	72 705 (39.8)	47 169 (25.8)
> 65	29 117 (36.1)	31 114 (38.6)	20 332 (25.2)	26 637 (40.0)	24 401 (36.7)	15 539 (23.3)
Province						
Eastern Cape	16 533 (34.6)	17 964 (37.6)	13 275 (27.8)	15 145 (34.6)	16 877 (38.5)	11 789 (26.9)
Free State	13 406 (35.0)	15 116 (39.5)	9 790 (25.6)	11 993 (35.3)	13 342 (39.3)	8 622 (25.4)
Gauteng	122 888 (36.6)	130 232 (38.8)	82 247 (24.5)	102 636 (35.6)	115 527 (40.1)	70 201 (24.3)
Kwazulu-Natal	37 863 (37.9)	36 785 (36.9)	25 136 (25.2)	30 705 (36.4)	31 718 (37.6)	21 974 (26.0)
Limpopo	13 029 (36.65)	13 077 (36.8)	9 439 (26.6)	11 250 (35.4)	12 428 (39.2)	8 068 (25.4)
Mpumalanga	23 139 (35.27)	25 013 (38.1)	17 453 (26.6)	21 388 (34.6)	24 549 (39.8)	15 826 (25.6)
North-West	18 818 (35.7)	20 155 (38.3)	13 700 (26.0)	17 416 (35.9)	18 869 (38.9)	12 277 (25.3)
Northern Cape	4 919 (32.1)	5 899 (38.6)	4 481 (29.3)	4 915 (32.9)	5 851 (39.2)	4 153 (27.8)
Western Cape	25 765 (34.9)	28 581 (38.7)	19 477 (26.4)	1 595 (36.5)	1 728 (39.6)	1 045 (23.9)
Not indicated	1 905 (39.8)	1 968 (41.2)	910 (19.0)	23 186 (35.0)	26 196 (39.5)	16 896 (25.5)

Table B.10 Antibiotic agents claimed from 2005 to 2012

	Number of medicine items claimed, n (%)								
Active substance	**2005 (N = 1 857 824)**	**2006 (N = 1 958 577)**	**2007 (N = 1 6387 41)**	**2008 (N = 1 289 027)**	**2009 (N = 1 639 988)**	**2010 (N = 1 436 642)**	**2011 (N = 1 151 168)**	**2012 (N = 1 014 657)**	**Relative change 2005 *vs.* 2012 (%)**
Aminoglycosides									
Gentamicin	6 668 (0.4)	6 933 (0.4)	7 108 (0.4)	5 875 (0.5)	7 696 (0.5)	6 056 (0.4)	4 948 (0.4)	5 378 (0.5)	+0.1
Amikacin	511(0.03)	758(0.04)	587 (0.04)	386(0.03)	302 (0.02)	341 (0.02)	194 (0.02)	189 (0.02)	-0.01
Kanamycin	337 (0.02)	311 (0.02)	271 (0.02)	191(0.01)	556 (0.03)	383 (0.03)	297 (0.03)	224 (0.02)	0.0
Streptomycin	126 (0.01)	139 (0.01)	172 (0.01)	112 (0.01)	156 (0.01)	130 (0.01)	126 (0.01)	106 (0.01)	0.0
Tobramycin	83 (0.0)	41 (0.0)	115 (0.01)	130 (0.01)	285 (0.02)	328 (0.02)	232 (0.02)	271 (0.03)	+0.03
Netilmicin	35 (0.0)	17 (0.0)	12 (0.0)	8 (0.0)	1 (0.0)	1 (0.0)	0 (0.0)	0(0.0)	0.0
Penicillins									
Amoxicillin/clavulanic	477 168 (25.7)	52 2050 (25.7)	432 832 (26.4)	353 407 (27.4)	450 654 (27.5)	37 7641 (26.3)	31 0051 (26.9)	273 433 (27.0)	+1.3
Amoxicillin	279 120 (15.0)	275 247 (14.1)	205 019 (12.5)	152 840 (11.9)	185 189 (11.3)	1 70315 (11.9)	144 699 (12.6)	129 926 (12.8)	-2.2
Amoxicillin/ Flucloxacillin	25 744 (1.4)	27 004 (1.4)	21 656 (1.3)	17 138 (1.3)	15 047 (0.9)	14 984 (1.0)	12 232 (1.1)	11 039 (1.1)	-0.3
Ampicillin/cloxacillin	11 285 (0.6)	11 236 (0.6)	9 956 (0.6)	7 430 (0.6)	7 368 (0.5)	5 801 (0.4)	4 336 (0.4)	3 679 (0.5)	-0.1
Cloxacillin	7 962 (0.4)	8 110 (0.4)	7 399 (0.5)	6 411 (0.5)	8 756 (0.5)	7 093 (0.5)	5 372 (0.5)	5 551 (0.6)	+0.2
Penicillin	6 566 (0.4)	7 255 (0.4)	5 368 (0.3)	4 532 (0.4)	5 032 (0.3)	3 179 (0.2)	2 863 (0.3)	2 576 (0.3)	-0.1
Ampicillin	5 320 (0.3)	5 365 (0.3)	3 707 (0.2)	2 360 (0.2)	2 680 (0.2)	1 439 (0.1)	1 354 (0.1)	1 111 (0.1)	-0.2
Benzathine penicillin	4 934 (0.3)	5 006 (0.3)	3 985 (0.2)	3 067 (0.2)	3 914 (0.2)	2 915 (0.2)	2 454 (0.2)	2 383 (0.2)	-0.1
Flucloxacillin	4 541 (0.2)	4 643 (0.2)	3 131 (0.2)	1 272 (0.1)	2 584 (0.2)	1 505 (0.1)	1 161 (0.1)	1 154 (0.1)	-0.1
Benzyl penicillin	1 634 (0.1)	1 575 (0.08)	1 595 (0.1)	1 596 (0.1)	2 504 (0.2)	1 730 (0.1)	132 (0.1)	1 297 (0.1)	+0.0
Procaine penicillin	1 711 (0.1)	2 539 (0.1)	2 008 (0.1)	2 221 (0.2)	4 329 (0.3)	3 960 (0.3)	3 031 (0.3)	3 618 (0.4)	+0.3
Piperacillin	6 (0.0)	3 (0.0)	1 (0.0)	1 (0.0)	3 (0.0)	0 (0.0)	9 (0.0)	0 (0.0)	0.0
Procaine penicillin	0 (0.0)	0 (0.0)	1 (0.0)	235 (0.02)	1 009 (0.06)	853 (0.1)	626 (0.05)	507 (0.05)	+0.05

Table B.10 Antibiotic agents claimed from 2005 to 2012 (continued)

	Number of medicine items, n (%)								
Active substance	**2005 (N = 1 857 824)**	**2006 (N = 1 958 577)**	**2007 (N = 1 638 741)**	**2008 (N = 1 289 027)**	**2009 (N = 1 639 988)**	**2010 (N = 1 436 642)**	**2011 (N = 1 151 168)**	**2012 (N = 1 014 657)**	**Relative change 2005 *vs.* 2012 (%)**
Cephalosporins									
Cefuroxime	85 217 (4.6)	91 266 (4.7)	83 217 (5.1)	60 658 (4.7)	82 182 (5.0)	70 734 (4.9)	51 504 (4.5)	45 058 (4.4)	-0.2
Cefpodoxime	75 412 (4.1)	80 871 (4.1)	72 552 (4.4)	48 194 (3.7)	80 021 (4.9)	73 651 (5.1)	57 495 (5.0)	47 443 (4.7)	+0.6
Cefaclor	32 399 (1.7)	25 859 (1.3)	11 817 (0.7)	6 171 (0.5)	6 768 (0.4)	5 260 (0.4)	3 936 (0.3)	3 090 (0.3)	-1.4
Cefprozil	23 376 (1.3)	22 501 (1.2)	21 564 (1.3)	13 088 (1.0)	18 137 (1.1)	12 627 (0.9)	8 335 (0.7)	6 957 (0.7)	-0.6
Cephalexin	18 708 (1.0)	13 801 (0.7)	10 351 (0.6)	6 329 (0.5)	8 280 (0.5)	6 952 (0.5)	5 715 (0.5)	4 875 (0.5)	-0.5
Cefotaxime	15 597 (0.8)	14 993 (0.8)	12 645 (0.8)	10 425 (0.8)	11 815 (0.7)	7 841 (0.6)	6 304 (0.6)	6 834 (0.7)	-0.1
Ceftriaxone	14 820 (0.8)	16 657 (0.9)	14 985 (0.9)	13 223 (1.0)	17 810 (1.1)	15 944 (1.1)	13 427 (1.2)	15 875 (1.6)	+0.8
Loracarbef	7 038 (0.4)	5 719 (0.3)	1 960 (0.1)	1 136 (0.1)	2 578 (0.2)	4 019 (0.3)	1 821 (0.2)	164 (0.02)	-0.38
Cefadroxil	5 819 (0.3)	4 991 (0.6)	4 453 (0.3)	3 254 (0.3)	2 570 (0.2)	1 435 (0.1)	780 (0.1)	257 (0.03)	0.0
Cefazolin	3 081 (0.2)	2 435 (0.1)	1 818 (0.1)	1 976 (0.2)	2 816 (0.2)	2 437 (0.2)	2 109 (0.2)	1681 (0.2)	0.0
Cephradine	2 557 (0.1)	3 695 (0.2)	2 354 (0.1)	1 877 (0.2)	2 212 (0.1)	1 080 (0.1)	728 (0.1)	544 (0.05)	-0.05
Cefixime	664 (0.04)	49 (0.002)	13 (0.0)	1 (0.0)	3 (0.0)	5 (0.0)	721 (0.1)	2 656 (0.3)	+0.26
Cefoxitin	213 (0.01)	330 (0.02)	469 (0.03)	136 (0.01)	27 (0.002)	28 (0.002)	17 (0.001)	30 (0.003)	-0.01
Ceftazidime	213 (0.01)	160 (0.01)	200 (0.01)	98 (0.01)	166 (0.01)	124 (0.01)	103 (0.01)	109 (0.01)	0.0
Ceftibuten	124 (0.01)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-0.01
Cefpirome	109 (0.01)	128 (0.01)	83 (0.01)	75 (0.01)	120 (0.01)	136 (0.01)	113 (0.01)	32 (0.003)	-0.01
Cefamandole	80 (0.004)	61 (0.003)	66 (0.0)	6 (0.0)	3 (0.0)	30 (0.002)	0 (0.0)	2 (0.0)	0.0
Cefradine	71 (0.004)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.0
Cephalothin	30 (0.002)	39 (0.002)	41 (0.002)	23(0.002)	3 (0.0)	13 (0.0)	36 (0.003)	4 (0.0)	0.0
Cefepime	8 (0.0)	21 (0.001)	35 (0.002)	24 (0.002)	28 (0.002)	27 (0.002)	13 (0.001)	24 (0.002)	0.0
Cefozolin	2 (0.0)	0 (0.0)	0 (0.0)	15 (0.0)	14 (0.001)	14 (0.001)	26 (0.002)	12 (0.001)	0.0
Cefalexin	0 (0.0)	0(0.0)	0 (0.0)	0 (0.0)	0 (0.0)	31 (0.002)	385 (0.03)	117 (0.01)	+0.01
Ceftazidime	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.o)	2 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.0

Table B.10 Antibiotic agents claimed from 2005 to 2012 (continued)

	Number of medicine items claimed, n (%)								
Active substance	**2005 (N = 1 857 824)**	**2006 (N = 1 958 577)**	**2007 (N = 1 638 741)**	**2008 (N = 1 289 027)**	**2009 (N = 1 639 988)**	**2010 (N = 1 436 642)**	**2011 (N = 1 151 168)**	**2012 (N = 1 014 657)**	**Relative change 2005 *vs.* 2012 (%)**
Fluoroquinolones									
Ciprofloxacin	157 264 (8.5)	170 663 (8.7)	150 828 (9.2)	120 524 (9.4)	148 966 (9.1)	137 261 (10.0)	105 945 (9.2)	93 574 (9.2)	+0.7
Levofloxacin	41 354 (2.2)	51 095 (2.6)	51 401 (3.1)	47 637 (3.7)	66 860 (4.1)	57 956 (4.0)	41 684 (3.6)	33 552 (3.3)	+1.1
Moxifloxacin	42 819 (2.3)	51 651 (2.6)	52 156 (3.2)	39 084 (3.0)	47 648 (2.9)	41 945 (2.9)	33 660 (2.9)	27 864 (2.8)	+0.5
Norfloxacin	22 989 (1.2)	19 875 (1.0)	15 525 (1.0)	11 661 (0.9)	12 469 (0.8)	10 500 (0.7)	8 689 (0.8)	6 685 (0.7)	-0.5
Ofloxacin	15 857 (0.9)	16 336 (0.8)	11 929 (0.7)	7 904 (0.6)	5 954 (0.4)	3 997 (0.3)	1 898 (0.2)	1 932 (0.2)	-0.7
Gatifloxacin	13 236 (0.7)	6 107 (0.3)	164 (0.01)	62 (0.01)	0 (0.0)	1 (0.0)	2 (0.0)	0 (0.0)	-0.7
Gemifloxacin	9 009 (0.5)	9 764 (0.5)	8 965 (0.6)	5 747 (0.5)	5 982 (0.4)	4 274 (0.3)	1 863 (0.2)	1 010 (0.1)	-0.4
Lomefloxacin	743 (0.04)	841 (0.04)	364 (0.02)	230 (0.02)	281 (0.02)	48 (0.003)	1 (0.0)	0 (0.0)	-0.04
Enoxacin	47 (0.003)	52 (0.003)	29 (0.002)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.0
Macrolides									
Clarithromycin	94 400 (5.1)	109 462 (5.6)	99 528 (6.1)	73 439 (5.7)	101 434 (6.2)	92 010 (6.4)	72 848 (6.3)	61 809 (6.1)	+1.0
Erythromycin	62 426 (3.4)	58 899 (3.0)	47 871 (2.9)	35 795 (2.8)	39 299 (2.4)	33 649 (2.3)	28 589 (2.5)	25 082 (2.5)	-0.9
Azithromycin	46 880 (2.5)	57 549 (2.9)	57 991 (3.5)	51 613 (4.0)	81 604 (5.0)	72 560 (5.1)	59 553 (5.2)	52 018 (5.1)	+2.6
Telithromycin	17 497 (0.9)	21 775 (1.1)	15 828 (1.0)	13 618 (1.1)	18 421 (1.1)	16 496 (1.2)	12 127 (1.1)	10 539 (1.0)	+0.1
Roxithromycin	16 093 (0.9)	17 237 (0.9)	12 790 (0.8)	8 842 (0.7)	7 095 (0.4)	5 446 (0.4)	3 311 (0.3)	2 546 (0.3)	-0.6
Tetracyclines									
Doxycycline	65 309 (3.5)	62 270 (3.2)	49 058 (3.0)	39 159 (3.0)	44 453 (2.7)	39 781 (2.8)	32 109 (2.8)	28 378(2.8)	-0.7
Oxytetracycline	9 507 (0.5)	8 996 (0.5)	6 517 (0.4)	5 201 (0.4)	5 514 (0.3)	3 611 (0.3)	2 638 (0.2)	2 179 (0.2)	-0.3
Minocycline	9 135 (0.5)	7 309 (0.4)	5 072 (0.3)	3 241 (0.3)	3 434 (0.2)	2 377 (0.2)	1 359 (0.1)	1 190 (0.1)	-0.4
Lymecycline	1 247 (0.7)	13 978 (0.7)	13 587 (0.8)	11 030 (0.9)	13 714 (0.8)	12 248 (0.9)	9 207 (0.8)	8 498 (0.8)	+0.1
Tetracycline	743 (0.04)	802 (0.04)	550 (0.03)	647 (0.05)	579 (0.04)	222 (0.02)	83 (0.01)	41 (0.004)	-0.04

Table B.10 Antibiotic agents claimed from 2005 to 2012 (continued)

	Number of medicine items claimed, n (%)								
Active substance	**2005 (N = 1 857 824)**	**2006 (N = 1 958 577)**	**2007 (N = 1 638 741)**	**2008 (N = 1 289 027)**	**2009 (N = 1 639 988)**	**2010 (N = 1 436 642)**	**2011 (N = 1 151 168)**	**2012 (N = 1 014 657)**	**Relative change 2005 *vs.* 2012 (%)**
Co-trimoxazole	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	23 (0.001)	0 (0.0)	0 (0.0)	0 (0.0)	0.0
Chloramphenicol	1 652 (0.09)	1 177 (0.06)	982 (0.06)	773 (0.06)	824 (0.05)	1 009 (0.07)	849 (0.07)	554 (0.05)	-0.04
Aztreonam	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	3 (0.0)	0 (0.0)	0.0
Ertapenem	4 (0.0)	15 (0.001)	18 (0.001)	20 (0.001)	50 (0.003)	52 (0.004)	58 (0.005)	48 (0.005)	0.0
Imipenem/cilastatin	7 (0)	3 (0.0)	2 (0.0)	2 (0.0)	11 (0.001)	13 (0.001)	7 (0.0)	3 (0.0)	0.0
Linezolid	0 (0.0)	0 (0.0)	52 (0.003)	0 (0.0)	85 (0.01)	59 (0.004)	37 (0.003)	41 (0.004)	0.0
Meropenem	5 (0.0)	1 (0.0)	7 (0.0)	8(0.0)	7 (0.0)	24 (0.002)	14 (0.002)	10 (0.001)	0.0
Trimethoprim	9 9074 (5.3)	110 909 (5.7)	93 980 (5.7)	86 867(6.7)	101 659 (6.2)	100 061(7.0)	85 757 (7.5)	78 889 (7.8)	+2.5

Table B.11 DDD/1 000 inhabitant/days of fluoroquinolones prescribed in patients above 18 years

Year	Generation	ATC Code	Fluoroquinolone	Total DDD	DDD/Inhabitant-year	DDD/1000 Inhabitant-days
2005	**1st**	J01MA06	Norfloxacin	85 229	0.06	0.18
	2nd	J01MA02	Ciprofloxacin	623 160	0.47	1.29
		J01MA04	Enoxacin	205	0.0002	0.0004
		J01MA14	Levofloxacin	221 663	0.17	0.46
		J01MA01	Ofloxacin	107 315	0.08	0.22
	3rd	J01MA16	Gatifloxacin	89 887	0.07	0.19
		J01MA14	Moxifloxacin	243 569	0.18	0.51
		Total		1 371 028	**1.04**	**2.85**
2006	**1st**	J01MA06	Norfloxacin	71 872	0.05	0.14
	2nd	J01MA02	Ciprofloxacin	707 654	0.52	1.42
		J01MA04	Enoxacin	242	0.0002	0.0005
		J01MA14	Levofloxacin	289 867	0.21	0.58
		J01MA01	Ofloxacin	113 000	0.08	0.23
	3rd	J01MA16	Gatifloxacin	41 879	0.03	0.08
		J01MA14	Moxifloxacin	298 009	0.22	0.60
		Total		1 522 523	**1.12**	**3.06**
2007	**1st**	J01MA06	Norfloxacin	55 252	0.05	0.14
	2nd	J01MA02	Ciprofloxacin	647 984	0.62	1.70
		J01MA04	Enoxacin	105	0.0001	0.0003
		J01MA14	Levofloxacin	310 741	0.30	0.82
		J01MA01	Ofloxacin	86 664	0.08	0.23
2007	**3rd**	J01MA16	Gatifloxacin	1 098	0.001	0.003
		J01MA14	Moxifloxacin	304 317	0.29	0.80
		Total		1 406 161	**1.35**	**3.69**
2008	**1st**	J01MA06	Norfloxacin	41 3625	0.05	0.13
	2nd	J01MA02	Ciprofloxacin	534 333	0.59	1.62
		J01MA14	Levofloxacin	311 392	0.35	0.95
		J01MA01	Ofloxacin	56 231	0.06	0.17
	3rd	J01MA14	Moxifloxacin	229 850	0.26	0.70
		Total		1173169	**1.31**	**3.57**
2009	**1st**	J01MA06	Norfloxacin	44 777	0.04	0.10
	2nd	J01MA02	Ciprofloxacin	669 510	0.55	1.51
		J01MA04	Enoxacin	7	0.00001	0.00002
		J01MA14	Levofloxacin	462 385	0.38	1.04
		J01MA01	Ofloxacin	42 295	0.03	0.10
		J01MA14	Moxifloxacin	276 778	0.23	0.62
		Total		1 495 752	**1.23**	**3.38**

Table B.11 DDD/1000 Inhabitant/days of fluoroquinolones prescribed in patients above 18 years (continued)

Year	Generation	ATC Code	Description	Total DDD	DDD/Inhabitan/year	DDD/1000 Inhabitant-days
2010	**1st**	J01MA06	Norfloxacin	38 979	0.03	0.09
	2nd	J01MA02	Ciprofloxacin	627 396	0.54	1.48
		J01MA14	Levofloxacin	413 515	0.36	0.97
		J01MA01	Ofloxacin	29 619	0.03	0.07
	3rd	J01MA16	Gatifloxacin	7	0.00001	0.00002
		J01MA14	Moxifloxacin	242 231	0.21	0.57
		Total		1 351 748	**1.16**	**3.18**
2011	**1st**	J01MA06	Norfloxacin	32 378	0.03	0.09
	2nd	J01MA02	Ciprofloxacin	491 032	0.47	1.29
		J01MA14	Levofloxacin	300 820	0.29	0.79
		J01MA01	Ofloxacin	14 130	0.01	0.04
	3rd	J01MA16	Gatifloxacin	14	0.00001	0.00004
		J01MA14	Moxifloxacin	195 186	0.19	0.51
		Total		1 033 561	**0.99**	**2.71**
2012	**1st**	J01MA06	Norfloxacin	25 076	0.02	0.07
	2nd	J01MA02	Ciprofloxacin	439 373	0.43	1.19
		J01MA14	Levofloxacin	249 192	0.25	0.67
		J01MA01	Ofloxacin	14 439	0.01	0.04
	3rd	J01MA14	Moxifloxacin	162 226	0.16	0.44
		Total			**0.88**	**2.41**

Table B.12 Cohen's *d*-value for the differences between the average DDDs per prescription per patient per year for fluoroquinolones prescribed in patients above 18 years, 2005 – 2012

	Ciprofloxacin						
	2005 (4.12 ± 3.21)	**2006 (4.41 ± 6.78)**	**2007 (4.47 ± 2.84)**	**2008 (4.59 ± 3.10)**	**2009 (4.65 ± 2.96)**	**2010 (4.71 ± 2.61)**	**2011 (4.77 ± 2.29)**
2006 (4.41 ± 6.78)	0.05	-					
2007 (4.47 ± 2.84)	0.09	0.04	-				
2008 (4.59 ± 3.10)	0.13	0.08	0.03	-			
2009 (4.65 ± 2.96)	0.14	0.09	0.05	0.02	-		
2010 (4.71 ± 2.61)	0.16	0.11	0.07	0.03	0.02	-	
2011 (4.77 ± 2.29)	0.18	0.12	0.08	0.05	0.03	0.01	-
2012 (4.84 ± 4.57)	0.19	0.14	0.10	0.07	0.05	0.03	0.02
	Levofloxacin						
	2005 (5.47 ± 4.57)	**2006 (5.79 ± 3.70)**	**2007 (6.15 ± 6.22)**	**2008 (6.65 ± 5.90)**	**2009 (7.04 ± 5.44)**	**2010 (7.23 ± 4.44)**	**2011 (7.30 ± 3.33)**
2006 (5.79 ± 3.70)	0.07	-					
2007 (6.15 ± 6.22)	0.14	0.07	-				
2008 (6.65 ± 5.90)	0.24	0.18	0.10	-			
2009 (7.04 ± 5.44)	0.32	0.26	0.18	0.08	-		
2010 (7.23 ± 4.44)	0.36	0.30	0.22	0.12	0.04	-	
2011 (7.30 ± 3.33)	0.38	0.31	0.24	0.13	0.05	0.01	-
2012(7.30 ± 3.72)	0.42	0.36	0.28	0.18	0.10	0.06	0.05
	Gatifloxacin						
	2005 (6.90 ± 1.56)	**2006 (6.98 ± 1.79)**	**2007 (7.13 ± 1.06)**	**2008 (7.05 ± 0.38)**	**2009**	**2010**	**2011**
2006 (6.98 ± 1.79)	0.05	-					
2007 (7.13 ± 1.06)	-	-	-				
2008 (7.05 ± 0.38)	-	-	-	-			

Table B.12 Cohen's *d*-value for the differences between the average DDDs per prescription per patient per year for fluoroquinolones prescribed in patients above 18 years, 2005 – 2012 (continued)

	Moxifloxacin						
	2005 (5.81 ± 4.03)	**2006 (5.89 ± 5.45)**	**2007 (5.96 ± 2.76)**	**2008 (6.00 ± 1.99)**	**2009 (5.91 ± 2.72)**	**2010 (5.86 ± 2.31)**	**2011 (5.87 ± 2.31)**
2006 (5.89 ± 5.45)	0.02	-					
2007 (5.96 ± 2.76)	0.04	0.02	-				
2008 (6.00 ± 1.99)	0.05	0.03	-	-			
2009 (5.91 ± 2.72)	0.03	-	-	0.03	-		
2010 (5.86 ± 2.31)	-	-	0.03	0.04	-	-	
2011 (5.87 ± 2.31)	-	-	0.03	-	-	-	-
2012 (5.90 ± 4.84)	0.3	-	-	0.03	-	-	-
	Norfloxacin						
	2005 (3.68 ± 2.75)	**2006 (3.74 ± 2.36)**	**2007 (3.67 ± 2.39)**	**2008 (3.66 ± 2.51)**	**2009 (3.69 ± 1.95)**	**2010 (3.79 ± 2.09)**	**2011 (3.81 ± 2.25)**
2006 (3.74 ± 2.36)	0.02	-					
2007 (3.67 ± 2.39)	0.00	0.03	-				
2008 (3.66 ± 2.51)	0.01	0.03	0.00	-			
2009(3.69 ± 1.95)	0.00	0.02	0.01	0.01	-		
2010 (3.79 ± 2.09)	0.05	0.02	0.05	0.05	0.04	-	
2011 (3.81 ± 2.25)	0.05	0.03	0.06	0.06	0.05	0.01	-
2012 (3.82 ± 2.28)	0.06	0.04	0.06	0.07	0.06	0.01	0.01

Table B.12 Cohen's *d*-value for the differences between the average DDDs per prescription per patient per year for fluoroquinolones prescribed in patients above 18 years, 2005 – 2012 (continued)

	Ofloxacin						
	2005 (7.22 ± 3.92)	**2006 (7.26 ± 3.53)**	**2007 (7.55 ± 3.31)**	**2008 (7.39 ± 3.94)**	**2009 (7.34 ± 3.75)**	**2010 (7.66 ± 5.75)**	**2011 (7.63 ± 5.75)**
2006 (7.26 ± 3.53)	-	-					
2007 (7.55 ± 3.31)	0.08	0.07	-				
2008 (7.39 ± 3.94)	0.04	-	-	-			
2009 (7.34 ± 3.75)	-	-	0.05	-	-		
2010 (7.66 ± 5.75)	0.11	0.10	-	0.07	0.08	-	
2011 (7.63 ± 5.75)	0.10	0.09	-	-	-	-	-
2012 (7.63 ± 4.57)	0.10	0.09	-	-	-	-	-

Table B.13 Cohen's *d*-value for differences between PDDs (mg) of fluoroquinolones prescriptions per year in patients 18 years and below stratified by age groups, 2005 - 2012

	Ciprofloxacin, ≥0, ≤5 years						
	2005 (1 062.47 ± 787.44)	**2006 (910.13 ± 592.80)**	**2007 (722 .13± 409.50)**	**2008 (776.83 ± 336.21)**	**2009 (821.22 ± 390.02)**	**2010 (818.93 ± 507.16)**	**2011 (814.17 ± 344.53)**
2006 (910.13 ± 592.80)	0.31	-					
2007 (722 .13± 409.50)	0.68	0.38	-				
2008 (776.83 ± 336.21)	0.57	0.27	-	-			
2009 (821.22 ± 390.02)	0.48	0.18	0.20	0.09	-		
2010 (818.93 ± 507.16)	0.49	0.18	0.19	0.08	-	-	
2011 (814.17 ± 344.53)	0.50	0.19	0.18	0.07	0.01	0.01	-
2011 (769.06 ± 296.86)	0.59	0.28	0.09	0.02	0.10	0.10	0.09

Table B.13 Cohen's *d*-value for differences between PDDs (mg) of fluoroquinolones prescribed per year in patients 18 years and below stratified by age groups, 2005 – 2012 (continued)

	Ciprofloxacin						
	>5, ≤12 years						
	2005 (1 223.55 ± 578.64)	2006 (1 009.23 ± 693.44)	2007 (858.88 ± 404.75)	2008 (886.08 ± 402.09)	2009 (1 004.52 ± 893.16)	2011 (851.81 ± 413.38)	2012 (872.01 ± 366.48)
2006 (1 009.23 ± 693.44)	0.16	-					
2007(858.88 ± 404.75)	0.28	0.12	-				
2008 (886.08 ± 402.09)	0.16	0.09	0.02	-			
2009 (1 004.52 ± 893.16)	0.17	0.00	0.11	0.09	-		
2010 (843.52 ± 392.40)	0.29	0.13	0.01	0.03	0.12	-	
2011 (851.81 ± 413.38)	0.28	0.12	0.11	0.03	0.12	0.01	-
2012 (872.01 ± 366.48)	0.27	0.11	0.01	0.01	0.10	0.02	0.02
	>12, ≤18 years						
	2005 (1 319.84 ± 959.03)	2006 (1 081 ± 857.74)	2007 (954.70 ± 376.04)	2008 (956.70 ± 376.04)	2009 (958.15 ± 345.79)	2010 (930.59 ± 339.88)	2011 (953.08 ± 328.73)
2006 (1 081.41 ± 857.74)	0.40	-					
2007 (954.70 ± 376.04)	0.62	0.21	-				
2008 (956.70 ± 376.04)	0.61	0.21	0.00	-			
2009 (958.15 ± 345.79)	0.61	0.21	0.01	0.00	-		
2010 (930.59 ± 339.88)	0.66	0.25	0.04	0.04	0.05	-	
2011 (953.08 ± 328.73)	0.62	0.22	0.00	0.01	0.01	0.04	-
2012 (945.65 ± 331.64)	0.63	0.23	0.01	0.02	0.02	0.03	0.01

Table B.13 Cohen's *d*-value for differences between PDDs (mg) of fluoroquinolones prescribed per year in patients 18 years and below stratified by age groups, 2005 – 2012 (continued)

	Gemifloxacin						
	>12, ≤18 years						
	2005 (367.41 ± 167.840)	**2006 (368.83 ± 262.10)**	**2007 (314.56 ± 41.53)**	**2008 (320.00 ± 0.00)**	**2009 (315.23 ± 33.22)**	**2010 (316.08 ± 27.08)**	**2011 (320.00 ± 0.00)**
2006 (368.83 ± 262.10)	0.01	-					
2007 (314.56 ± 41.53)	0.39	0.40	-				
2008 (320.00 ± 0.00)	0.35	0.36	0.04	-			
2009 (315.23 ± 33.22)	0.39	0.40	0.00	0.04	-		
2010 (316.08 ± 27.08)	0.38	0.39	0.01	0.03	0.01	-	
2011 (320.00 ± 0.00)	0.35	0.36	0.04	0.00	0.04	0.03	-
2012 (309.33 ± 53.33)	0.43	0.44	0.04	0.08	0.04	0.05	0.08
	Levofloxacin						
	>5, ≤12 years						
	2005 (548.73 ± 491.54)	**2006 (469.50 ± 202.02)**	**2007 (511.75 ± 256.14)**	**2008 (542.78 ± 234.70)**	**2009 (546.11 ± 236.04)**	**2010 (367.38 ± 135.62)**	**2011 (448.53 ± 213.46)**
2006 (469.50 ± 202.02)	0.29	-					
2007 (511.75 ± 256.14)	0.13	0.15	-				
2008 (542.78 ± 234.70)	0.02	0.27	0.11	-			
2009 (546.11 ± 236.04)	0.01	0.28	0.12	0.01	-		
2010 (367.38 ± 135.62)	0.66	0.37	0.52	0.64	0.65	-	
2011 (448.53 ± 213.46)	0.36	0.08	0.23	0.34	0.35	0.29	-
2012 (389.25 ± 119.15)	0.58	0.29	0.44	0.52	0.57	0.08	0.21

Table B.13 Cohen's *d*-value for differences between PDDs (mg) of fluoroquinolones prescribed per year in patients 18 years and below stratified by age groups, 2005 – 2012 (continued)

	Levofloxacin						
	>12, ≤18 years						
	2005 (534.48 ± 348.38)	**2006 (505.21 ± 246.53)**	**2007 (530.83 ± 228.63)**	**2008 (575.49 ± 217.08)**	**2009 (611.64 ± 232.21)**	**2010 (593.06 ± 210.01)**	**2011 (594.25 ± 220.31)**
2006 (505.21 ± 246.53)	0.29	-					
2007 (530.83 ± 228.63)	0.13	0.10	-				
2008 (575.49 ± 217.08)	0.17	0.29	0.18	-			
2009 (611.64 ± 232.21)	0.31	0.43	0.33	0.15	-		
2010 (593.06 ± 210.01)	0.25	0.36	0.25	0.07	0.08	-	
2011 (594.25 ± 220.31)	0.24	0.36	0.26	0.08	0.07	0.00	-
2012 (595.09 ± 208.72)	0.25	0.33	0.26	0.08	0.07	0.01	0.00
	Moxifloxacin						
	>5 and ≤ 12 years						
	2005 (474.62 ± 246.18)	**2006 (449.00 ± 356.48)**	**2007 (392.67 ± 40.82)**	**2008 (400.00 ± 0.00)**	**2009 (391.39 ± 45.99)**	**2010 (760.00 ± 130.11)**	**2011 (647.50 ± 211.77)**
2006 (449.00 ± 356.48)	0.13	-					
2007 (392.67 ± 40.82)	0.42	0.29	-				
2008(400.00 ± 0.00)	0.39	0.25	0.04	-			
2009 (391.39 ± 45.99)	0.43	0.25	0.01	0.04	-		
2010 (760.00 ± 130.11)	0.43	0.29	0.00	0.04	0.00	-	
2011 (647.50 ± 211.77)	0.40	0.27	0.00	0.02	0.03	0.03	-
2012 (766.67 ± 115.47)	0.39	0.25	0.00	0.00	0.04	0.04	0.02

Table B.13 Cohen's *d*-value for differences between PDDs (mg) of fluoroquinolones prescribed per year in patients 18 years and below stratified by age groups, 2005 – 2012 (continued)

	Moxifloxacin						
	>12 and ≤ 18 years						
	2005 (581.36 ± 181.97)	**2006 (441.82 ± 229.78)**	**2007 (394.10 ± 66.65)**	**2008 (396.06 ± 34.50)**	**2009 (398.90 ± 27.87)**	**2010 (396.44 ± 29.11)**	**2012 (397.52 ± 23.63)**
2006 (441.82 ± 229.78)	0.20	-					
2007 (394.10 ± 66.65)	0.27	0.07	-				
2008 (396.06 ± 34.50)	0.27	0.07	0.00	-			
2009 (398.90 ± 27.87)	0.26	0.06	0.01	0.00	-		
2010 (396.44 ± 29.11)	0.27	0.07	0.00	0.00	0.00	-	
2011 (396.63 ± 31.54)	0.27	0.07	0.00	0.00	0.00	0.00	-
2012 (397.52 ± 23.63)	0.27	0.06	0.00	0.00	0.00	0.00	0.00
	Norfloxacin						
	>5 and ≤ 12 years						
	2005 (985.74 ± 316.99)	**2006 (898.27 ± 308.48)**	**2007 (784.80 ± 129.52)**	**2008 (761.45 ± 129.52)**	**2009 (760.00 ± 130.11)**	**2010 (699.26 ± 198.88)**	**2011 (647.50 ± 211.77)**
2006 (898.27 ± 308.48)	0.36	-					
2007 (784.80 ± 129.52)	0.84	0.47	-				
2008 (761.45 ± 129.52)	0.93	0.57	0.10				
2009 (760.00 ± 130.11)	0.94	0.58	0.10	0.01			
2010 (699.26 ± 198.88)	1.19	0.83	0.36	0.26	0.25		
2011 (647.50 ± 211.77)	1.41	1.04	0.57	0.47	0.47	0.22	
2012 (766.67 ± 115.47)	0.91	0.55	0.08	0.02	0.03	0.28	0.50

Table B.13 Cohen's *d*-value for differences between PDDs (mg) of fluoroquinolones prescribed per year in patients 18 years and below stratified by age groups, 2005 – 2012 (continued)

	>12 and ≤ 18 years						
	2005 (1 143.29 ± 668.92)	**2006 (987.19 ± 529.29)**	**2007 (773.46 ± 106.70)**	**2008 (783.40 ± 82.43)**	**2009 (772.16 ± 106.43)**	**2010 (764.23 ± 124.44)**	**2012 (779.10 ± 88.11)**
2006 (987.19 ± 529.29)	0.38	-					
2007 (773.46 ± 106.70)	0.90	0.52	-				
2008 (783.40 ± 82.43)	0.88	0.50	0.02	-			
2009 (772.16 ± 106.43)	0.91	0.53	0.00	0.03	-		
2010 (764.23 ± 124.44)	0.93	0.54	0.02	0.05	0.02	-	
2011 (750.20 ± 139.97)	0.96	0.58	0.06	0.08	0.05	0.03	-
2012 (779.10 ± 88.11)	0.89	0.51	0.52	0.01	0.02	0.04	0.07
	Ofloxacin						
	>5 and ≤ 12 years						
	2005 (1 214. 37 ± 503.09)	**2006 (912.49 ± 375.63)**	**2007 (689.96 ± 144.51)**	**2008 (669.96 ± 144.51)**	**2009 (656.00 ± 209.55)**	**2010 (347.83 ± 227.38)**	**2011 (436.36 ± 196.33)**
2006 (912.49 ± 375.63)	0.77	-					
2007 (689.96 ± 144.51)	1.33	0.56	-				
2008 (669.96 ± 144.51)	1.38	0.62	0.05	-			
2009 (656.00 ± 209.55)	1.42	0.65	0.09	0.03	-		
2010 (347.83 ± 227.38)	2.20	1.43	0.87	0.82	0.78	-	
2011 (436.36 ± 196.33)	1.97	2.21	0.64	0.59	0.56	0.22	-
2012 (250.00 ± 100.00)	2.45	1.68	1.12	1.06	1.03	0.25	0.47

Table B.13 Cohen's *d*-value for differences between PDDs (mg) of fluoroquinolones prescribed per year in patients 18 years and below stratified by age groups, 2005 – 2012 (continued)

	>12 and ≤ 18 years						
	2005 (1 195.69 ± 549.88)	**2006 (958.23 ± 478.81)**	**2007 (717.29 ± 135.46)**	**2008 (685.98 ± 158.52)**	**2009 (711.18 ± 152.60)**	**2010 (599.74 ± 241.56)**	**2011 (671.30 ± 223.70)**
2006 (958.23 ± 478.81)	0.58	-					
2007 (717.29 ± 135.46)	1.16	0.59	-				
2008 (685.98 ± 158.52)	1.24	0.66	0.08	-			
2009 (711.18 ± 152.60)	1.18	0.60	0.01	0.06	-		
2010 (599.74 ± 241.56)	1.45	0.87	0.29	0.21	0.27	-	
2011 (671.30 ± 223.70)	1.27	0.70	0.11	0.04	0.10	0.17	-
2012 (647.47 ± 206.67)	1.33	0.76	0.17	0.09	0.15	0.12	0.06

Table B.14 Cohen's *d*-value for difference between average PDDs (mg) of fluoroquinolones claimed by patients 18 years and below according to prescribers' specialty

Year		**Ciprofloxacin**			
2005		**General medical practice (1 334.43 ± 1 103.74)**	**Paediatrician (657.34 ±314.91)**	**Specialist (820.95 ± 450.49)**	**Pharmacotherapist (750.00 ± 288.68)**
	Paediatrician (657.34 ± 314.91)	0.63	-		
	Specialist (820.95 ± 450.49)	0.48	0.15	-	
	Pharmacotherapist (750.00 ± 288.68)	0.55	0.09	0.07	-
	Other (743.53 ± 432.09)	0.55	0.08	0.07	0.01
2006		**General medical practice (1 088.65 ± 845.01)**	**Paediatrician (658.42 ± 286.47)**	**Specialist (709.72 ± 302.41)**	**Pharmacotherapist (666.67 ± 288.86)**
	Paediatrician (658.42 ± 286.47)	0.52	-		
	Specialist (709.72 ± 302.41)	0.46	0.06	-	
	Pharmacotherapist (666.67 ± 288.86)	0.51	0.01	0.05	-
	Other (733.37 ± 280.68)	0.43	0.09	0.03	0.08

Table B.14 Cohen's *d*-value for difference between average PDDs (mg) of fluoroquinolones claimed by patients 18 years and below according to prescribers' specialty (continued)

Year	Ciprofloxacin				
2007		General medical practice (943.98 ± 370.03)	Paediatrician (737.03 ± 349.05)	Specialist (802.75 ± 245.21)	Pharmacotherapist (500.00 ± 0.00)
	Paediatrician (737.03 ± 349.05)	0.57	-		
	Specialist (802.75 ± 245.21)	0.39	0.18	-	
	Pharmacotherapist (500.00 ± 0.00)	1.24	0.65	0.83	-
	Other (726.38 ± 282.98)	0.59	0.03	0.21	0.62
2008		General medical practice (956.85 ± 383.97)	Paediatrician (753.46 ± 287.31)	Specialist (682.05 ± 287.73)	Pharmacotherapist (1 000.00 ± 0.00)
	Paediatrician (753.46 ± 287.31)	0.54	-		
	Specialist (682.05 ± 287.73)	0.73	0.19	-	
	Pharmacotherapist (1 000.00 ± 0.00)	0.11	0.65	0.84	-
	Other (796.02 ± 276.65)	0.43	0.11	0.30	0.54
2009		General medical practice (982.78 ± 229.70)	Paediatrician (713.25 ± 323.80)	Specialist (759.85 ± 282.07)	Pharmacotherapist
	Paediatrician (713.25 ± 323.80)	0.23	-		
	Specialist (759.85 ± 282.07)	0.19	0.00	-	
	Other (760.51 ± 284.03)	0.19	0.14	0.00	-
	Pharmacotherapist	-	-	-	-
2010		General medical practice (926.48 ± 351.79)	Paediatrician (806.22 ± 510.31)	Specialist (759.85 ± 282.07)	Pharmacotherapist
	Paediatrician (806.22 ± 510.31)	0.34	-		
	Specialist (759.85 ± 282.07)	0.52	0.19	-	
	Other (785.07 ± 267.38)	0.39	0.06	0.13	-
	Pharmacotherapist	-	-	-	-

Table B.14 Cohen's *d*-value for difference between average PDD of fluoroquinolones claimed by patients 18 years and below according to prescribers' specialty (continued)

Year	Ciprofloxacin				
2011		General medical practice (943.19 ± 346.84)	Paediatrician (746.75 ± 297.84)	Specialist (787.26 ± 312.41)	Pharmacotherapist
	Paediatrician (746.75 ± 297.84)	0.57	-		
	Specialist (787.26 ± 312.41)	0.45	0.12	-	
	Other (901.35 ± 329.12)	0.12	0.45	0.33	-
	Pharmacotherapist	-	-	-	-
2012		General medical practice (940.79 ± 340.61)	Paediatrician (766.32 ± 340.61)	Specialist (865.96 ± 256.28)	Pharmacotherapis
	Paediatrician (766.32 ± 340.61)	0.52	-		
	Specialist (865.96 ± 256.28)	0.22	0.30	-	
	Other (740.94 ± 269.91)	0.60	0.08	0.37	
	Pharmacotherapist	-	-	-	
	Gemifloxacin				
2007		General medical practice (314.37 ± 41.37)	Paediatrician (320.00 ± 00)	Specialist (186.87 ± 188.56)	Pharmacotherapist
	Paediatrician (320.00 ± 00)	0.13	-		
	Specialist (186.87 ± 188.56)	3.04	3.18	-	
	Other (320.00 ± 0.00)	0.13	0.00	3.18	
	Pharmacotherapist	-	-	-	
	Norfloxacin				
2007		General medical practice (777.77 ± 103.23)	Paediatrician (800.00 ± 0.00)	Specialist (600.00 ± 282.84)	Pharmacotherapist
	Paediatrician (800.00 ± 0.00)	3.53	-		
	Specialist (600.00 ± 282.84)	1.66	1.87	-	
	Other (710.00 ± 168.01)	0.63	2.89	1.03	-
	Pharmacotherapist	-	-	-	-

Table B.14 Cohen's *d*-value for difference between average PDD of fluoroquinolones claimed by patients 18 years and below according to prescribers' specialty (continued)

	Ofloxacin				
2005		General medical practice (1 212.82 ± 534.31)	Paediatrician (585.67 ± 301.70)	Specialist	Pharmacotherapist (400.00 ± 00)
	Paediatrician (585.67 ± 301.70)	1.18	-		
	Pharmacotherapist (400.00 ± 0.00)	1.53	0.53	-	-
	Other (465.31 ± 196.49)	1.41	0.23	-	-
	Specialist	-	-	-	
2006		General medical practice (956.23 ± 461.90)	Paediatrician (600.00 ± 230.94)	Specialist	Pharmacotherapist (577.78 ± 384.90)
	Paediatrician (600.00 ± 230.94)	0.78	-		
	Pharmacotherapist (577.78 ± 384.90)	0.82	0.05	-	-
	Other (506.12 ± 201.84)	0.98	0.20	-	-
	Specialist	-	-	-	
2007		General medical practice (715.10 ± 134.44)	Paediatrician (715.10 ± 134.44)	Specialist (800.00± 00)	Pharmacotherapist
	Paediatrician (715.10 ± 134.44)	-	-		
	Specialist (800.00± 00)	0.62	-	-	
	Other (577.78 ± 210.82)	1.01	-	1.63	-
	Pharmacotherapist	-	-	-	-
2009		General medical practice (715.00 ± 148.79)	Paediatrician (344.00 ± 125.22)	Specialist (800.00 ± 00)	Pharmacotherapist
	Paediatrician (344.00 ± 125.22)	2.49	-		
	Specialist (800.00 ± 00)	0.57	3.05	-	
	Pharmacotherapist	-	-	-	-
	Other (700.00 ± 200.00)	0.10	2.38	0.67	-

Table B.14 Cohen's *d*-value for difference between average PDD of fluoroquinolones claimed by patients 18 years and below according to prescribers' specialty (continued)

	Ofloxacin				
		General medical practice (581.58 ± 247.34)	**Paediatrician (200.00 ± 0.00)**	**Specialist (600.00 ± 282.84)**	**Pharmacotherapist**
2010	**Paediatrician (200.00 ± 0.00)**	1.59	-		
	Specialist (600.00 ± 282.84)	0.08	1.67	-	
	Pharmacotherapist	-	-	-	-
	Other	-	-	-	-