Exploring Trends in Antibiotic Use and Resistance in a District, Regional and Tertiary Hospital in the uMgungundlovu District.

By

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Submitted in fulfilment of the academic requirements for the degree of Master of Pharmacy in the discipline of Pharmaceutical Sciences in the School of Health Sciences, University of KwaZulu-Natal, Durban.

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A dissertation submitted to the School of Health Sciences, College of Health Science, University of KwaZulu-Natal, Westville Campus, for the degree of Master of Pharmacy (Pharmacy Practice).

This is the dissertation in which the research is presented as a discrete research publication, with an overall introduction and final summary.

This is to certify that the content of this dissertation is the original research work of Miss Ayesha Desai.

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DECLARATION

I **Ayesha Desai** declare that

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LIST OF ABBREVIATIONS

CDC	Center for Disease Control and Prevention
E. coli	*Escherichia coli*
EML	Essential Medicines List
GAP	Global Action Plan
HGT	Horizontal Gene Transfer
IPC	Infection, Prevention and Control
MRSA	Methicillin Resistant Staphylococcus Aureus
MSSA	Methicillin Susceptible Staphylococcus Aureus
NDoH	National Department of Health
NHLS	National Health Laboratory Service
NICD	National Institute for Communicable Diseases
SAASP	South African Antibiotic Stewardship Programme
S. aureus	*Staphylococcus aureus*
STG	Standard Treatment Guideline

ABSTRACT

Antibiotics play an important role in overcoming life-threatening bacterial infections. However, the increasing rate of antibiotic resistance is a serious threat to public health. Undoubtedly the indiscriminate use of antibiotics plays a role in the emergence of resistance. The objective of this study was to identify the trends in antibiotic use and resistance at three public sector hospitals at three different levels of healthcare in the uMgungundlovu district, i.e., a district hospital, a regional hospital and a tertiary hospital. The antibiotics indicated for the treatment of infections caused by *Escherichia coli* (*G*ram-negative bacteria*)* and *Staphylococcus aureus* (Gram-positive bacteria) were investigated. Yearly antibiotic consumption data was calculated as Defined Daily Dose (DDD) per 1 000 inhabitants and percentage susceptibility was analysed based on susceptible and non-susceptible isolates for each antibiotic. There was a general trend of reduced antibiotic susceptibility as the levels of healthcare increased attributed to the fact that more severe and complex infections are treated at the higher levels of healthcare and require greater quantities of and/or broader spectrum antibiotics. For treatment of infections caused by *S. aureus* antibiotic use generally increased as the level of healthcare increased. Azithromycin was the most frequently used while linezolid was the least used antibiotic and showed the highest levels of susceptibility across all levels of healthcare. *S. aureus* showed the lowest level of susceptibility to cloxacillin across all the levels of healthcare and was indicative of the prevalence of methicillin-resistant *S. aureus* (MRSA). When antibiotic use was correlated with resistance, cloxacillin displayed a downward trend in use from 2014 to 2016 while cloxacillin resistance increased from 2014 to 2015 followed by a decrease in resistance in 2016 indicating that resistance is a function of time and use and that the lag time between the decrease in use and a corresponding decrease in resistance is not predictable and varies for different antibiotics in different healthcare settings. In contrast, azithromycin showed a steady decline in resistance although use increased over the three years (2014-2016). In the case of the treatment of infections caused by *E. coli* there was a general trend of the greater use of narrow spectrum antibiotics at the lower district and regional levels while the broad-spectrum antibiotics were used more frequently at a tertiary level. Trimethoprim-sulphamethoxazole was used the most, whereas colistin was used the least. Contrary to expectations, there were higher susceptibility levels to third and fourth generation cephalosporins and meropenem at a tertiary level than regional level. *E. coli* showed lowest levels of susceptibility to ampicillin and highest level of susceptibility to levofloxacin across all levels of healthcare. When antibiotic use was correlated with resistance, antibiotics that were used frequently (sulphamethoxazole-trimethoprim, amoxicillin clavulanic acid and ampicillin) displayed high levels of resistance over the three years. Trimethoprim-sulphamethoxazole use decreased slightly over the years

however resistance remained high. The same trend was observed with amoxicillin clavulanic acid and ampicillin use and resistance indicating possible co-selection of resistance by the use of other classes of antibiotics. This study added to the body of knowledge that there exists a link between the use of antibiotics and resistance, albeit not a direct causal one. Quantifying antibiotic use and identifying trends in resistance associated with antibiotic consumption assists prescribers and policy makers to improve antibiotic use, guide antibiotic stewardship programmes and optimise antibiotic policies and guidelines.

CONTENTS

LIST OF FIGURES AND TABLES

TABLES

FIGURES

CHAPTER 1. INTRODUCTION AND LITERATURE REVIEW

1.1 INTRODUCTION

Antibiotics are agents that kill or inhibit the growth of bacteria. Soil bacteria or fungi produce them naturally. The exposure of antibiotics to bacteria causes the microbes to either die or adapt. Thus antibiotic resistance occurs through these protective, adaptive bacterial mechanisms (Microbiology Society, 2017). The development of antibiotics dates back to between 1937 and 1940. Those were the years, in which the discovery of sulphonamides and penicillin (the first two usable antibiotic agents) revolutionized medicine in many aspects. The development of antibiotics was considered "a turning point in human history" (Davies & Davies, 2010). Antimicrobial agents became widely available and accessible and were used to treat common infections, many of which were not caused by bacteria. In 1945, during an interview with the New York Times, Sir Alexander Fleming (the scientist who discovered penicillin) said that based on laboratory research he had conducted, the inappropriate use of penicillin could lead to resistant mutant forms of *Staphylococcus aureus*. True to his word – bacterial resistance to the antibiotic was witnessed at a phenomenal rate. During the first year of use of penicillin a number of strains of *S. aureus* had become resistant to the antibiotic (Alanis, 2005). Resistance was thought to be a problem pertaining to hospitalised patients only. However, resistance was soon recorded in the outpatient setting where resistant bacteria contributed to the development of community-acquired infections (Alanis, 2005). Newer antibiotics were required to overcome the resistance that had developed and this led to the development of several other antibiotic classes. Over time there have been over 17 classes of antibiotics that were discovered and produced. However, bacteria have developed one or more resistance mechanisms against each class over time (Davies & Davies, 2010).

Resistance itself is costly to governments and patients, and is threatening the effectiveness of health delivery worldwide. The pipeline of drug discovery is not optimal and the incentive to develop new antibiotics is reduced (WHO, 2001). The discovery of new antibiotics declined from the 1990s. The Food and Drug Administration (FDA) of America gave 29 new approvals for antibiotics during the 1990s while the first decade of the 2000s saw only 9 new approvals (The PEW Charitable Trusts, 2016). Shareholders of pharmaceutical companies that undertake the development of new medicines expect high returns on their investments in these companies. New antibiotic development is increasingly expensive and in many cases may require 10-14 years for approval for clinical use followed by 20 years of patent life.

Globally there has been a reduction in cost effective and quality assured novel therapeutic agents (Alanis, 2005).

All antibiotics need to be conserved. One way of doing so is by using newer and broad-spectrum antibiotics sparingly. This does however lead to a domino effect. The restriction on sales and use of novel antibiotics will lead to a decrease in the generation of revenues. This in turn leads to a decrease in the interest and investment in research and development. There is the proposed model of delinking profits from product sales and pharmaceutical return on investment to try and tackle the growing concern of reduced investment in antimicrobial research and development (Outterson et. al., 2016). Scientific barriers in medicine discovery, regulatory challenges and decreased returns on investments have led to pharmaceutical companies scaling down on antibiotic research (The PEW Charitable Trusts, 2016). There is the need for the continuous discovery of novel antibiotics. Interventions are also required to slow down and contain the progression of antibiotic resistance using a multi-disciplinary approach (Ndihokubwayo et. al, 2013). Diverse, multi-faceted strategies need to be explored in order to contain the escalating antibiotic resistance challenge.

The development of antibiotic resistance can be attributed to the indiscriminate use of antibiotics in human, animal and environmental health by human beings and resistance may thus be seen as a man-made situation that has been "superimposed on nature" (Lewis, 2013). The excessive use of antibiotics has exerted selection pressure and has contributed to the emergence of resistance that has reached unprecedented levels globally. In the presence of an antibiotic the microbes find methods of adaptation, becoming resistant. The resistant bacterial cell multiplies conferring resistance onto subsequent cells (Microbiology Society, 2017).

National antibiotic resistance containment policies and stewardship programmes need to be continually revised and implemented in the healthcare system, to optimize antibiotic use with an overall aim of reducing use, in order to attempt to contain antibiotic resistance. Optimizing the use of antimicrobials is one of the strategic objectives of the Global Action Plan (GAP) on Antimicrobial Resistance formulated by the tripartite alliance of the World Health Organization (WHO), the Food and Agriculture Association of the United Nations (FAO) and the Organization for Animal Health (OIE). Objective 4 of the GAP speaks to optimizing the use of antimicrobial medicines in both human and animal health. WHO recognizes the need for evidence-based prescribing and dispensing of antibiotics. There is a dearth of data on antibiotic use in humans from lower-income countries (World Health Organization, 2014).

In order for evidence-based strategies to be developed, monitoring of antibiotic use and prescribing patterns need to be conducted to track the nature and extent of antibiotic use, specifically misuse, overuse and/or underuse of such agents. One such way is through adopting medicine utilization studies within health facilities. The ultimate goal of a medicine utilization study is to assess whether therapy is rational or appropriate. One way of representing medicine utilization is by calculating defined daily doses (DDDs). DDD is a statistical measure of medicine consumption defined by the WHO Collaborating Centre (WHOCC) for Drug Statistics. Figures are presented as number of DDDs per 1 000 inhabitants per day for outpatients and as number of DDDs per 100 bed-days for inpatients (WHO, 2003). DDD is a unit of measurement that is independent of the price of the medicine and is used by researchers to analyse trends in medicine consumption allowing for comparisons between different medicines and/or different health environments (WHO, 2011). The unit of measurement has been used since the early 1970s and has been found suitable for medicine utilization comparisons to be made nationally and internationally, to evaluate long-term trends in medicine use and to assess the impact of certain events in healthcare on medicine use. DDDs further provide denominator data in investigating medicine safety (WHO, 2011).

This comparative study quantified antibiotic consumption in terms of defined daily doses per 1 000 inhabitants (DDDs) by using central pharmaceutical stores depot issuing data obtained for three hospitals at different levels of care, i.e., district, regional and tertiary. Trends in antibiotic susceptibility at the three levels of healthcare were also explored using microbiology data from existing databases at the hospitals in question. DDDs per 1 000 inhabitants were then correlated with antibiotic resistance patterns. This allowed basic comparisons on antibiotic consumption and resistance between health care facilities at different levels of healthcare deliver.

1.2 LITERATURE REVIEW

1.2.1 Antibiotic Resistance: A Global Public Health Concern

In the presence of antibiotics, bacteria are either killed or carry resistant genes that enable them to survive. The surviving bacteria then replicate, sometimes at a rapid speed. These replicated bacteria then become the dominant microbes within their population leading to sustained resistance. The misuse, overuse and/or inappropriate use of antibiotics are drivers for the development and escalation of antibiotic resistance (NIH, 2011).

The Antimicrobial Resistance Review Report commissioned by the government of the United Kingdom both analyses antibiotic resistance as a global problem and proposes steps that can be taken to tackle the problem (O'Neil, 2014). The report highlighted the alarming evidence of global resistance:

- 99 000 deaths occur each year in the United States (US) which are caused by hospital acquired infections from resistant bacteria.
- Antimicrobial resistant organisms account for 25 000 deaths per year in Europe.
- In a developing country like Pakistan, resistant bacteria cause 71% of neonatal infections.
- The majority of hospital infections in Peru and Bolivia are due to antimicrobial resistant bacteria.

O'Neil (2014) posits that if antimicrobial resistance is neglected, it is estimated that by the year 2050 more than 10 million people will die per year due to resistant infections.

In 2012 Kinmang'a conducted a situational analysis of antimicrobial resistance in Africa on the premise that the influx of large quantities of antibiotics entering African countries through the advancement of technology and resources has the potential to promote antibiotic resistance and cause lifesaving medicines to become ineffective. With the use of PubMed online database, 103 articles were sourced. Research articles on antimicrobial resistance in African countries were analysed. Root-causes of antimicrobial resistance were identified this included the lack of human resources in the healthcare sector in sub-Saharan Africa, inadequate laboratory facilities coupled with inadequately trained staff to isolate pathogens and perform sensitivity tests leading to non-evidence-based empirical treatment of infectious diseases. The study argued that empirical treatment contributed to the emergence of resistant strains of bacteria as many African countries lacked adequate guidelines to ensure good prescribing practices. There was insufficient local data to assist in promoting antibiotic

stewardship programmes in healthcare facilities (Kinmang'a, 2012). This situational analysis helps us to recognise that antimicrobial resistance is a growing problem in developing countries and more specifically on the African continent.

1.2.2 The Development of Antimicrobial Resistance

The development of resistance is a consequence of selection pressure which occurs when the use of antimicrobial agents applies "selection pressure" by killing the susceptible bacteria thus allowing resistant microorganisms to survive and thrive. There are two main types of resistance. The first type is intrinsic (innate or inherent) resistance and the second type is acquired resistance.

1.2.2.1 Intrinsic Resistance

This is an innate ability of the bacterial species to withstand activity of the antimicrobial agent on the microorganism. It is often resistance that is developed by the bacterial population prior to use by the human population (Martinez, 2009). Thus this type of resistance is independent of antimicrobial exposure. Such resistance includes "lack of affinity of the drug for the bacterial target, inaccessibility of the drug into the bacterial cell, extrusion of the drug by chromosomally encoded active exporters (efflux pump), and, innate production of enzymes that inactivate the drug" (Michigan State University, 2011). For example, vancomycin resistance in Gram-negative bacteria is as a result of the inability of the antibiotic molecule to penetrate the Gram-negative outer membrane (Holmes et al., 2015). Another example is mycoplasmas that do not have an outer cell wall and are therefore intrinsically resistant to β-lactams and glycopeptides as they target the cell wall (Reygaert, 2016). Knowledge on this form of resistance is important to prevent inappropriate and/or ineffective treatment.

1.2.2.2 Acquired Resistance

In contrast, acquired resistance is where isolates, which were previously susceptible, acquire mechanisms of resistance. There is a change in the genetic composition of the bacteria resulting in a previously effective antimicrobial agent being rendered in-effective (Stokowski, 2010). Acquired resistance involves a selection process (Holmes et al., 2015). Some examples of acquired resistance are as follows:

- Drug inactivation: Bacteria acquire gene-encoded enzymes such as β-lactamases that

inactivate or destroy the antimicrobial agent before they reach the target site.

- Cell wall changes: Mutations in genes responsible for outer membrane porin regulation or expression render the outer membrane impermeable to the antimicrobial agent.
- Bypass targets: Mutations in the bacterial DNA change the target enzyme in a metabolic pathway resulting in bypassing of the primary target site (Stokowski, 2010).

1.2.3 Global Action Plan on Antimicrobial Resistance

In May 2014 the World Health Assembly (WHA) endorsed the development of the "Global Action Plan on Antimicrobial Resistance" (GAP) by the WHO. It is an action plan that forms a basis for countries to develop and improve their own national action plans for the containment of antibiotic resistance. The primary goal of the GAP is to achieve the successful treatment and, where possible, prevention of infectious diseases. This is to be achieved by encouraging the responsible use of quality assured medicines and improved accessibility to those in need of them. There are five strategic objectives outlined in the GAP:

1. "To improve awareness and understanding of antimicrobial resistance through effective communication, education and training.
2. To strengthen the knowledge and evidence base through surveillance and research.
3. To reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures.
4. To optimize the use of antimicrobial medicines in human and animal health.
5. To develop the economic case for sustainable investment that takes account of the needs of all countries and to increase investment in new medicines, diagnostic tools, vaccines and other interventions." (World Health Organization, 2015)

Strategic objective 2 addresses the need for surveillance. Knowledge can be strengthened through an inter-disciplinary approach. Co-operation from national government, intergovernmental organizations, along with non-governmental organizations, industry and academia play a pivotal role in generating knowledge through surveillance and research. Research is imperative in understanding and supporting the implementation of objectives one, three and four. Studies must include effective antimicrobial stewardship programmes in the one health approach. WHO has identified some of the gaps in knowledge as being:

1. Lack of knowledge on incidence, prevalence and pathogenic and geographical patterns concerning antibiotic resistance. Such information should be promptly available in order for evidence based diagnosis and treatment of patients to take place. This knowledge will also assist in guiding local, national and regional policymaking and subsequently the effectiveness of the interventions can be

monitored.

2. There is the need for improved understanding of how resistance is spread within and between humans, animals and agriculture. Furthermore, researchers need to stay abreast on emerging resistance and the underlying mechanisms involved. There is the need for the rapid characterization of newly emerging resistance and the understanding of the underlying mechanisms. This will assist in ensuring that surveillance and diagnostic methods and tools are kept up to date. Investment in research and development thus needs to be encouraged (World Health Organization, 2014). One example is that of the WHO Regional Office for Africa development of a guideline for assisting countries in establishing and/or improving laboratory-based surveillance. The guideline highlights the components required for laboratory-based surveillance and subsequent steps involved in establishing these facilities. There are steps provided for antimicrobial resistance surveillance of meningitis, bacteraemia and enteric epidemic-prone diseases (World Health Organization, 2013). Implementation of the guideline will encourage evidence-based prescribing of antibiotics and will also assist in creating a surveillance database reference that is regionally specific. The application of evidence-based prescribing will also lead to optimization of antibiotic use.
3. A greater degree of research needs to be done on treatment and prevention of prevalent bacterial infections. This knowledge is required especially in low resource settings.
4. Research from translational studies need to be used in treatment development, diagnostic tools, vaccines amongst other primary interventions.
5. In agriculture and aquaculture – alternatives to non-therapeutics uses of antibiotics have to be identified.
6. Costs involved in the antimicrobial resistance pandemic as well as the costs versus benefits of the Global Action Plan need to be weighed and assessed.

When it comes to antibiotic resistance in pathogens of major public health concern there are several inconsistencies. There are no internationally recognised standards for the collection of data and reporting thereof on resistance in humans. Furthermore, there is no suitable forum for the sharing of surveillance data globally. There is also the need for agreed upon standards across medical, veterinary and agricultural sectors. In 2013, European Union Member States had published a strategic research agenda. The WHO encourages the use of the agenda as a preliminary framework for the development of a global strategic research agenda.

Strategic objective 4 of the GAP speaks to the optimizing of antimicrobial medicines in both human and animal health. Antibiotic use in humans, animals and agriculture is increasing

rapidly (World Health Organization, 2014). If the indiscriminate use of antibiotics is not addressed, it is estimated that within 35 years, drug-resistant bacterial infections will result in 10 million deaths annually. Africa and Asia will account for 4.1 and 4.7 million of these deaths respectively (Mendelson & Matsoso, 2015). 76% of the global increase in antibiotic use during the years 2000 – 2010 is collectively attributable to BRICS (Brazil, Russia, India, China, South Africa) (Boeckel et. al, 2014). The increasing use of antibiotics can be attributable to over-prescribing, over the counter sales and in some countries antibiotics are widely available via the Internet. Regulations surrounding the distribution, quality and use of antibiotics need to be strengthened. Relevant stakeholders must be encouraged to invest in research and development. Healthcare workers need to be more vigilant when it comes to the prescribing and dispensing of antibiotics. It is important for them to identify the source of infection and not be subject to patient pressure to prescribe antibiotics unnecessarily. Sub optimal patient and health care provider compliance, substandard antibiotics in humans and veterinary practice coupled with the inappropriate or unregulated use of antibiotics are contributing factors to growth of antibiotic resistance. Regulations have to be strictly enforced. The standard of care should be primarily evidence based prescribing and dispensing. Therefore countries need to invest wisely in effective, rapid and affordable diagnostic tools to encourage evidence-based prescribing in human and animal health (World Health Organization, 2014).

1.2.4 South African Antimicrobial Resistance Framework

After much focus was placed on antimicrobial resistance at the WHA in 2014, in October 2015 the National Department of Health (NDoH) in collaboration with the South African Antibiotic Stewardship Programme (SAASP) held a summit for the adoption of an Antimicrobial Resistance National Strategic Framework (Brink, 2015). The Director General of Health, Precious Matsoso highlighted that in 2013, in South Africa, there was a case of multi-drug resistant (MDR) *Klebsiella pneumoniae* that was found to be resistant to all available antibiotics. In South Africa susceptibility data for the period 2012 to 2014 showed that resistance in *K. pneumoniae to* third generation cephalosporin was 32%, while fluoroquinolone resistance increased from 28-30% in 2013 (Faure, 2015). This emphasizes the urgent call to act upon antimicrobial resistance. The national strategic framework sheds light on the drivers of resistance. It talks of the unnecessary high quantities of antibiotics being used. Prescribers rely heavily on broad-spectrum antibiotics as opposed to streamlining treatment with narrow-spectrum, bacteria-specific antibiotics. The goals of the national strategy are:

1. To define the principles and short to medium term interventions needed to preserve the effectiveness of antimicrobials for future generations.
2. To improve the appropriate use of antibiotics in human and animal health;
3. To improve the effective management of antibiotic resistant organisms and to prevent their transmission.
4. To create an enabling environment for the successful and sustainable implementation of the strategic objectives (National Department of Health, 2014).

The goals are then followed by four strategic objectives:

1. Strengthen, coordinate and institutionalise interdisciplinary efforts.
2. Optimise surveillance and early detection of antimicrobial resistance.
3. Enhance infection prevention and control.
4. Promote appropriate use of antimicrobials in human and animal health (National Department of Health, 2014).

When reviewed broadly, the strategic objectives focus on surveillance, infection prevention and control (IPC) and antimicrobial stewardship. Surveillance incorporates national surveillance of resistant bacteria, antimicrobial use, medication error reporting structures and antimicrobial quality. Monitoring and improving of IPC must be carried out in both the community and at hospital level. Antimicrobial stewardship is grounded by policies and protocols, which include formulary restrictions, antimicrobial pre-authorisation and prescription forms and national prescribing guidelines. Stewardship in terms of point of care encompasses performing the correct diagnosis coupled with the correct choice of antimicrobial given at the optimum dose. Prescribers also need to de-escalate and discontinue antimicrobial agents when it is safe and advisable to do so. There are strategic enablers underpinning these objectives and are as follows:

1. Legislative and policy reform for health systems strengthening – Policies need to set the minimum standards for health care quality systems and processes. In animal health, stringent control over the use of antibiotics needs to be implemented.
2. Education – Antimicrobial resistance strategies should be encompassed in the student curricula of all healthcare and allied healthcare professionals. Continuing Professional Development (CPD) programmes should include antimicrobial resistance and the importance of antimicrobial stewardship. Public health drives and campaigns must be held to create awareness and improve the understanding surrounding antimicrobial resistance.

3. Communication – Patient advocacy, introducing the topic in the media and partnering with industry are recommended.
4. Research - Translational research should be encouraged and adopted in improving and creating diagnostic tools, antimicrobial stewardship interventions and IPC (National Department of Health, 2014.

The overall purpose of the National Antimicrobial Resistance Framework is to serve as a guideline in managing antimicrobial resistance. It highlights actions incumbent upon the NDoH and all other relevant stakeholders to limit resistant microbial infections and to improve and achieve optimal patient care (National Department of Health, 2014).

1.2.5 Surveillance of Antibiotic Use and Resistance.

When formulating an effective response to antibiotic resistance it is important to assess the scope of the problem. One such way is through surveillance. Moreover, the importance of surveillance is acknowledged and highlighted as an objective in both the GAP and the South African Antimicrobial Resistance Framework. Surveillance includes the collecting and analysing of data. This, in the healthcare setting, allows for the monitoring and detection of possible threats and outbreaks. In turn this will assist in generating an action plan to reduce and/or prevent future health threats. Surveillance of resistance data includes having access to microbiology laboratory susceptibility data of isolated bacteria. This would also provide information on the extent of resistance identified in the bacterial species or identified isolates. Changes in resistance patterns can also be monitored over time. In England, hospital laboratories are encouraged to upload their microbiology sensitivity data to a national database (Johnson, 2015). The system focuses on capturing trends of resistance in *S. aureus*, Enterococci, *Streptococcus pneumoniae, P. aeruginosa, E. coli, K. pneumoniae* and Enterobacter species. This information is then readily available. It is a large amount of useful data collected on a continuous basis and also provides a vast geographical coverage of information (Johnson, 2015). In United States of America's (USA), the White House's National Strategy to Combat Antibiotic-Resistant Bacteria talks to the importance of surveillance. Analysing and reporting of antibiotic resistant bacteria is important for evidence-based decisions to be made. Surveillance data should be available for each country as well as globally (Washington, 2014). In the USA, The Centers for Disease Control and Prevention (CDC) collect data on antibiotic resistant infections, the cause of the infection and factors that may have contributed to the patient acquiring the infection. Informed strategies are then developed to prevent the spread of the infection and resistant bacteria (United States,

2013).

In South Africa, the National Institute for Communicable Disease (NICD) undertakes antibiotic resistance surveillance. They have developed a two-tier reporting system. The first one is laboratory-based surveillance of antimicrobial resistance (LARS) via the Group for Enteric, Respiratory and Meningeal Surveillance in South Africa (GERM SA) (NICD, 2017). GERM SA is a nationwide network of microbiology laboratories both in the public and private sector that participates in laboratory based surveillance of pathogens of public health importance (NICD, 2017). The second reporting system involves electronic surveillance from the Corporate Data Warehouse (CDW). CDW is where data is stored from laboratories serving all public health sector hospitals in South Africa. Surveillance reports are then made available on the NICD website. An example of the latest surveillance reported is the Antimicrobial Resistance Surveillance from Sentinel Public Hospitals, South Africa, 2015. The objective of the surveillance programme was to record the number of isolates of selected pathogens on a monthly basis from selected hospitals. Antimicrobial susceptibility to the most important treatment regimens recorded by pathogen and hospital was established. Sixteen hospitals from across the country participated in the study. Isolate data of bloodstream infections for the period January 2015 to December 2015 was extracted for: *Acinetobacter baumannii* complex, *Enterobacter cloacae* complex, *Escherichia coli, Enterococcus faecalis, Enterococcus faecium, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Staphylococcus aureus* (Perovic &Chetty, 2015). Antibiotic susceptibility data was analysed by the CDW. Results of each bacterial species included the total number of isolates, their susceptibility profiles and percentage susceptibility to selected antibiotics. It is important to monitor trends in antibiotic use and resistance in order for evidence-based decisions to be made. It provides information for policy makers and heads of departments involved to make informed decisions regarding future antibiotic guidelines and recommendations.

1. 2. 6 Antibiotic stewardship

Coupled with surveillance is the need for antibiotic stewardship programmes to optimise antimicrobial use. Antibiotic stewardship involves evidence-based interventions to work towards improving the appropriate use of antibiotics, assist in containing antimicrobial resistance and work on reducing the spread of multi drug resistant organisms (APIC, 2017). Antibiotic stewardship involves a range of clinical interventions to try and reduce the unnecessary use of antimicrobial agents. The goal of stewardship programmes is to assist in

reducing the emergence of antimicrobial resistance caused by selective pressure and to optimize patient safety (Pulcini et al., 2017). In 2015, "A Pocket Guide to Antibiotic Prescribing for Adults in South Africa" was published on behalf of the South African Antibiotic Stewardship Programme (SAASP). A guideline to effective antibiotic stewardship is provided in the manual**.** Firstly it is important to ascertain whether prescribing of an antibiotic is required. This is to look for evidence of a bacterial infection. This includes checking whether the patient has a fever, inflamed skin, tachypnoea, dysuria as well as any raised inflammatory markers (e.g. C Reactive Protein, erythrocyte sedimentation rate). If a bacterial infection is suspected then only is the patient started on antibiotics. Cultures must be performed before the antibiotic is administered. This allows for de-escalation to a narrow spectrum antibiotic once antibiotic susceptibility results are made available. If there is a clear site of infection then a specimen from the site of infection must be taken and sent to the laboratory for culture testing. If the site of infection cannot be established then a blood culture is performed. When choosing empiric treatment it is important to target the most likely pathogen of the infection. For example, if a urinary tract infection is suspected it is likely that it is gram-negative bacilli causing the infection. The antibiotic of choice is then the narrowest spectrum antibiotic implicated in treating a gram-negative bacilli infection. Stewardship includes assessing antibiotic resistance. The pharmacist needs to check if there is known colonization with resistant pathogen, Health Care Associated Infection (HCAI) or the patient has had a course of antibiotics recently. The pharmacist must ensure that there is no likelihood of contra indications or drug-drug interactions. Mono-therapy is favoured unless there is no alternate to combination therapy or if combination therapy produces a favourable synergistic outcome. Pharmacists should also ensure the correct dose and suitable route of administration is being used. Pharmacists should encourage physicians to switch from intravenous to oral antibiotics whenever possible. When dealing with severe infections the appropriate antibiotic treatment must be commenced as soon as possible within the first hour of the antibiotic being prescribed to the reduce mortality rate. Antibiotic therapy must be monitored on a daily basis (Wasserman et. al, 2015). Stewardship can be implemented in healthcare facilities by creating antimicrobial prescription charts and enforcing appropriate prescribing in accordance to the Essential Medicines List (EML) and Standard Treatment Guidelines (STGs) (National Department of Health, 2014). Vigilant monitoring should lead to a decrease in antibiotic consumption and optimising the use thereof (Messina et. al, 2017). A pharmacist-driven study was conducted in 47 private hospitals in South Africa. The study assessed the impact of antibiotic stewardship on improving antibiotic use. The study was made up of three phases: pre-implementation, implementation and post-implementation. It was over five year conducted between October 2009 and September 2014. The primary goal was to attain a 10% reduction in antibiotic use and to launch antibiotic stewardship

programmes in the facilities that did not have any. The stewardship programme monitored five key "process measures":

1. Recording the number of cases where antibiotic treatment was commenced before cultures had been done.
2. Recording cases where an antibiotic was used for more than seven days.
3. Recording cases where antibiotic treatment was given for more than fourteen days.
4. Recording cases where more than four antibiotics were used concurrently for treatment.
5. Redundant antibiotic treatment – where more than one antibiotic was used with the same spectrum of activity (Brink et. al, 2016).

During the pre-implementation phase it was found that 41 out of the 47 hospitals did not have an antibiotic stewardship programme in place. Healthcare professionals received training on the five targeted process measures. Furthermore, none of the hospitals had local antibiotic guidelines or policies. The implementation phase was conducted between February 2011 and January 2013. Antibiotic consumption was measured and recorded as DDD per 100 patient days. Pharmacists initiated and carried out necessary interventions. Pharmacists also provided monthly reports based on the outcomes of the five process measures. Statistics reflected that nearly 1 in 15 prescriptions required an intervention to be carried out – in all cases the prescriber was consulted first. 39% of these interventions were related to prolonged duration of antibiotic treatment (Brink et. al, 2016).

A similar study was conducted in the public sector to evaluate the outcomes from the Groote Schuur Hospital Antibiotic Stewardship Programme initiative. The objective of the study was to report antibiotic consumption and implicated costs over a four-year period based on information retrieved from the hospital's antibiotic stewardship programme. The hospital has a dedicated antibiotic prescription chart and weekly ward rounds dedicated to antibiotic stewardship. Outcomes measured included changes in antibiotic consumption and costs involved. The trends in the request of laboratory cultures, in patient mortality and re-admission rates were also measured. Antibiotic use data during the intervention period (01/01/2012 – 31/12/2015) was compared to a control period (01/01/2011 – 31/12/2011). In 2011 antibiotic consumption was 1046 DDD per 1000 patient days. In 2012 there was no change recorded, however, in the subsequent years (2013 – 2015) there was an overall 18% decrease in antibiotic consumption. Reduction was noticed most in intravenous antibiotics. The inflation – adjusted cost of antibiotics for 2011 was R 2 191 594. This amount decreased for every subsequent year during the study period. A sum of R 3 326 340 was saved over the four years. In terms of request for laboratory tests – during the study the number of requests for full blood count (FBCs) and blood cultures increased from 162 to 2014 and 24.7 to 30.9

per 1000 patient bed days. Study outcomes revealed that antibiotic stewardship programmes could be introduced into the public sector and could improve antibiotic consumption (Boyles et. al, 2017).

1.2.7 Defined Daily Dose

Medicine utilization studies date back to the 1960s. During those years the importance of comparing medicine use between regions and countries was brought to public attention. Work done by Arthur Engel and Pieter Siderius (1960) in the medicine utilization field reflected differences in the sale of antibiotics in six European countries between 1966 and 1967. This led to the first meeting on medicine utilization held by the WHO and saw the development of the WHO European Drug Utilization Research Group (DURG) (Kumar et. al., 2013). The goal of medicine utilization studies is to assess whether the medicine therapy in question is rational or not. For comparative purposes medicine audits should be conducted using the unit of measurement developed by researchers in Northern Ireland, Norway and Sweden known as defined daily dose (DDD) (WHO, 2003). Defined Daily Doses (DDD) is a statistical measure, and is defined by the WHO as "the assumed average maintenance dose per day for a drug used for its main indication in adults" (WHOCC, 2016). In other words, DDD is a measure of the amount of medicine that an adult will receive each day for the treatment of an implicated infection. DDD is not to be confused with the therapeutic dose for the medication (University of Dundee, 2017). Therapeutic dose is the amount of medication required to produce a desired effect in terms of treatment (Trevor et. al, 2013). This standardised unit allows for trends and comparisons of medicine consumption to be made at an international level (WHO, 2017). Medicine consumption is expressed as a rate and therefore it must include a denominator and time unit. For outpatient-data DDD per 1 000 inhabitant days is used and for in-patient hospital data DDD per 100 bed days is used. DDDs are assigned for most medicines with a few exceptions such as topical products, sera, vaccines, antineoplastic agents, allergan extracts, contrast media, local and general anaesthetics (WHOCC, 2016). Like with any method DDD comes with both advantages and disadvantages. It is advantageous in that it is published by the WHO and internationally recognised. DDDs are not often changed and therefore this allows for assessments of antibiotic use to be made over time. The measurement provides the ability to make comparisons with regards to antibiotic use in a standardised way. DDD may not however be a true reflection for a particular infection and no DDDs have been established yet for paediatric dosing. There can also be an underestimation of antibiotic use due to the fact that alterations to dosing regimens is not taken into account (University of Dundee, 2017).

In South Africa, the use of DDD as a unit of measure for medicine consumption dates back to 1996. A preliminary study was carried out in South Africa to evaluate the use of DDD as a measure of medicine consumption. The study was conducted in Port Elizabeth. DDD per 1000 registered patients per day and the cost per DDD was calculated. The study focused on antipsychotic, antidepressant, hypnotic and anxiolytic medication. Researchers concluded that the DDD was a useful methodology to measure medicine consumption irrespective of what type of medicine class was under investigation. DDD is essential in making national and international comparisons (Truter et. al, 1996). It is also seen as a useful technique to promote rational and cost-effective use of medicines in South Africa.

1.2.8 The use of the DDD methodology to study antibiotic resistance

A study was conducted to evaluate the effects of macrolide use on erythromycin resistance in *Streptococcus pyogenes (S. pyogenes)*. This study was conducted in Finland with consumption and resistance data for the years 1997 – 2001. During 1997 – 2001 annual resistance rates varied from 1.2% to 39%. Annual macrolide and azithromycin use for the years 1995 – 2000 varied from 1.15 to 2.85 DDD per 1000 inhabitant days respectively. Statistically analysed results reflected a significant association between regional erythromycin resistant *S. pyogenes* and use of macrolides. No significant association was found between erythromycin resistance *S. pyogenes* and azithromycin use. Researchers suggested that this could be due to the fact that selection pressure in azithromycin is not as strong as that of other macrolides used in the treatment of *S. pyogenes*. When taking into consideration a lag period – the higher the previous antibiotic consumption was, the higher the level of resistance witnessed. The relationship between use and resistance is a complex one (Bergman et al., 2004). Exploring trends in use and resistance gives us some understanding on the topic and significant conclusions can be proposed

During 2000 – 2010 there was an outbreak of carbapenem resistant OXA- 48 producing *K. pneumoniae* in a renal unit of a hospital in London, United Kingdom. This led to researchers conducting a study of the use of meropenem in this facility. Meropenem consumption data for the years 2005-2014 were interpreted as predictors of the OXA-48 producing *K. pneumoniae*. Consumption data was represented as DDD per 100 occupied bed days (OBD). Data was captured for 4 years prior and 5 years after the intervention to contain the outbreak. This included restricting carbapenem prescribing. This led to the updating of prescribing policies to restrict the use of meropenem only in the presence of aminoglycoside – resistant

microorganisms. Results reflected that meropenem consumption was highly correlated with the production of OXA-48 organisms. By performing a time series analysis researchers were able to predict future potential outbreaks. Taking into consideration a 1 year lag period – meropenem consumption was most positively correlated with the incidence of OXA-48-producing *K. pneumoniae.* Considering the positive correlation it was important to review the impact of an antimicrobial stewardship intervention on meropenem usage. Pre intervention meropenem consumption showed a year – on – year increase (6.30 to 25.65 DDD/100 OBD). Post intervention meropenem consumption revealed a year – on – year decrease (25.65 to 10.00 DDD/100 OBD). Researchers concluded reducing meropenem usage reduced the selective pressure towards carbapenem resistance. This study advocates monitoring antimicrobial use as it assists in forecasting the emergence of outbreaks and consequent trends in the prevalence of antimicrobial resistance. It also assists in evaluating the impact of interventions by reviewing pre and post intervention results (Gharbi, et al., 2015).

The incidence of healthcare acquired (HCA) MRSA and Vancomycin Resistant Enterococci (VRE) was noted to be on the rise in Taiwan. Few studies had investigated the association between linezolid, fusidic acid or tigecycline exposure and the prevalence of MRSA and VRE. A study was carried out in Taiwan using an 11-year period database (2000 – 2010). The aim of the study was to investigate "the correlation between consumption of antibiotics including vancomycin, teicoplanin, linezolid, tigecycline, fusidic acid and daptomycin and the incidence of HCAI-MRSA and HCAI-VRE. Annual consumption data of vancomycin, teicoplanin, linezolid, fusidic acid, tigecycline and daptomycin were retrieved from the pharmacy database and presented as DDD/ 1000 patient-days. There was no significant correlation between the increased use of vancomycin, teicoplanin, tigecycline, fusidic acid and the prevalence of HCAI-MRSA. A positive correlation was noted between teicoplanin use and HCAI-VRE as well as tigecycline use and HCAI-VRE. Over the study period the use of teicoplanin and linezolid had increased significantly whilst the use of the other agents remained relatively stable. Researchers speculated that prescribers favoured the use of teicoplanin or linezolid over vancomycin when treating MRSA, as they have fewer side effects. Such studies allow us to explore correlations between antimicrobial use and resistance. Where no significant correlations are found it helps us to understand that we should not rely solely on correlations as a method of quantification of use and resistance (Lai et. al., 2015).

The use of carbapenems and its correlation with the prevalence of *A. baumanni* was surveyed in a hospital in Turkey. The study was conducted from 1 May 2011 to 28 February 2013. The study consisted of 2 study observations: carbapenem non – restricted period and a

carbapenem-restricted period. During the restriction period the use of carbapenems was restricted to patients where alternate therapy was not possible. Carbapenem consumption and the number of patients with multi drug resistant (MDR) *A. baumanni* were evaluated. A total of 10.82 DDD/ 100 ICU bed days of carbapenem was used when no restrictions were in place. During the carbapenem restriction period this rate dropped to 6.95 DDD/ 100 ICU bed days. During the carbapenem non-restrictive phase, 3.98% MDR *A. baumanni* were detected whereas this figure dropped to 1.82% when restrictions on carbapenem use were enforced. Results show that there was a 2.24 fold higher prevalence of MDR *A. baumanni* in a non-controlled environment. This study showed that antibiotic restriction results in a decline in resistance. Researchers were able to achieve a 2-fold reduction the outbreak of a life threatening infection (Ogutlu, 2014).

A study was conducted over a 5-year period (1 January 2000 to 31 December 2004) to measure antibiotic use and antibiotic resistance patterns in an intensive care burn department in a hospital in Tunisia. The increasing use of antibiotics in hospitals and the subsequent economic implications led researchers to investigate antibiotic use in this hospital. Antimicrobial density (antibiotic in grams converted to DDD and number of hospitalization days) was calculated for imipenem, ceftazidime, ofloxacin, ciprofloxacin and piperacillin-tazobactam. Results reflected a relationship between ceftazidime use and ceftazidime resistant *K. pneumoniae*. There was no significant relationship between the use of ceftazidime and resistance to *P. aeruginosa* but a relationship was witnessed with the consumption of ciprofloxacin and the rate of ciprofloxacin resistant *P. aeruginosa*. It was concluded that monitoring antibiotic consumption and correlating it with resistance is a necessity in order to implement policies to reduce the existing global antimicrobial resistance burden (Messadi et. al, 2008). Monitoring of use correlated with resistance allows us to assess where problem areas lie and where resources need to be used to try and resolve these problems.

It was only as late as 2005 that the first study on the relationship between antibiotic consumption and antibiotic use was carried out in the Lagos University Teaching Hospital in Nigeria. Prior to the study there had been no real attempts to investigate the appropriateness of antibiotic use in Nigerian hospitals, hence the need for the study. The study was conducted between January 2005 and June 2006, to improve researchers' knowledge on the relationship between antibiotic consumption rates and antibiotic resistance rates of uro-pathogens. Nigeria reported inappropriate prescribing of antibiotics by medical practitioners and the abuse of antibiotics by patients. The names of antibiotics usually used to treat urinary tract infections (UTIs) and corresponding number of grams per unit per package were entered into a spread sheet. Thereafter the number of packages of each antibiotic consumed between January 2005

and June 2005, and July 2005 and December 2005, and January 2006 and June 2006 was recorded. DDD for each antibiotic for the 6-monthly periods was generated and a 6-monthly comparison of antibiotic resistance and consumption rates were analysed using Pearson's correlation coefficient. The antibiotics most commonly prescribed during the study period were ciprofloxacin and amoxicillin-clavulanic acid whilst trimethoprim-sulphamethoxazole was the least prescribed. Interestingly, resistance rates were highest for trimethoprim-sulphamethoxazole followed by amoxicillin-clavulanic acid (Oduyebo et. al, 2008). Selection pressure from the use of one antibiotic class may co-select resistance to other antibiotic classes as resistance genes are frequently co-carried on mobile genetic elements (Essack, et. al, 2005). A fairly short study period was used however significant trends and correlation between resistance and consumption were identified (Oduyebo et. al, 2008).

From the international and local literature reviewed for the purposes for this study. It is evident that antimicrobial surveillance studies in Africa are still in the inception phase. Evidence based studies are required for effective policy interventions to take place (Osman et. al., 2016). As presented in the literature above, the importance of surveillance, research and optimizing the use of antibiotics has been recognised both internationally (WHO GAP) and locally (SA AMR Framework). Optimizing antibiotic use by antibiotic stewardship programmes have proven successful in studies conducted in South Africa's private and public sectors. Co-ordinated efforts are required to update knowledge through research and surveillance, strictly enforce existing policies and address indiscriminate antibiotic use. A study of this nature has not been conducted in the proposed district (uMgungundlovu district). Data obtained from this study may be used to compare and contrast antibiotic consumption and resistance patterns at other South African public healthcare facilities. This study is a preliminary step in evaluating the current antibiotic use and associated resistance burden on a district level. DDD's, as a standard unit of measurement, has proven effective in all the studies reviewed. The literature presented serves as a motivation to explore trends in antibiotic use and resistance patterns. DDD is approved and widely used as a unit of measure for representing antimicrobial consumption. Studies cited have successfully explored probable trends between antimicrobial use and resistance and have proven effective in capturing the epidemiological interpretation of antibiotic consumption on resistance.

1.3 AIMS AND OBJECTIVES

This study aimed to quantify and explore trends in antibiotic use and resistance in three public hospitals in the uMgungundlovu district at different levels of healthcare using defined daily doses (DDDs)/1000 inhabitants as consumption data and antimicrobial susceptibility data from existing databases.

The study had the following objectives:

1. To calculate DDDs (as a measure of consumption) in a tertiary, regional and district, hospital in uMgungundlovu using depot-issuing data.
2. To compare and contrast antibiotic consumption at the different levels of healthcare in the district.
3. To compare and contrast antibiotic susceptibility at the different levels of healthcare in the district.
4. To demonstrate, whether there are any significant associations between antibiotic consumption (presented as DDD) and resistance from microbiology data obtained from the hospitals.

1.4 OVERVIEW OF STUDY DESIGN AND METHODOLOGY AND

Ethical Considerations

A request was made to the Head of the Department of Health (DoH) of KwaZulu-Natal, the Head of Pharmaceutical Service of Kwa Zulu Natal and the District Health Manager of the uMgungundlovu district to conduct the study in the uMgungundlovu district. The University of KwaZulu-Natal's Human and Social Sciences Research Ethics Committee granted ethical approval to conduct the study. Upon successful consent from all parties involved the Head of the Provincial Medical Supply Centre provided depot-issuing data that delineated the medicines and their quantities issued to the hospitals by central stores. The National Institute for Communicable Diseases (NICD) provided the necessary microbiology information, i.e. antimicrobial susceptibilities of *Escherichia coli* and *Staphylococcus aureus* as representative Gram-negative and Gram-positive bacteria respectively from the hospitals in question for the period 2014-2017.

Study Site

Study data was from three hospitals in the uMgungundlovu District. These hospitals were selected in order for comparisons to be made at different levels of healthcare (district, regional and tertiary hospitals). The district provides a health service to 10% of the KwaZulu-Natal province which is an estimated 1 052 730 individuals. uMgungundlovu district has also been selected as a pilot district for National Health Insurance (NHI) to be implemented in South Africa (DoH, 2016).

Study design

The study sought to investigate trends between antibiotic consumption and resistance at different levels of healthcare. An observational, retrospective study was undertaken. Aggregated data was used. Provincial depot issuing data which lists the medicines and the quantities issued to the hospitals by central stores was used to calculate the DDDs. Antibiotic susceptibility data that was required for the hospitals was obtained from the NICD.

Antibiotic Use

Consumption data received from the DoH for the years 2014 to 2016 was filtered to find the data required for the antibiotics in question. This data was used to calculate DDD using the WHO/ATC DDD consumption tool. Step-by-step Guidelines provided by WHO Collaborating Centre for Drug Statistics Methodology on their website was used to accurately capture data on the electronic Antimicrobial Consumption (AMC) Tool which automatically calculated DDD once data was successfully entered. The pathogens under investigation were *E. coli (*Gram-negative bacteria*)* and *S. aureus* (Gram-positive bacteria). The antibiotics that were selected to calculate DDD were therefore based on their indication for infections caused by the bacteria mentioned. The antibiotic panel for E. *coli* was constituted by amoxicillin-clavulanic acid, ampicillin, amikacin cefepime, cefotaxime, ceftazidime, ceftriaxone, ciprofloxacin, colistin, gentamicin, imipenem, levofloxacin, meropenem, piperacillin-tazobactam, trimethoprim-sulphamethoxazole. The antibiotic panel for *S. aureus* was constituted by azithromycin, cefoxitin, cloxacillin, clindamycin, linezolid and vancomycin.

Antibiotic Resistance

Susceptibility data for *E .coli* and *S. aureus* was obtained from the NICD for the years 2014 – 2017 in the resistant, intermediate, susceptible (R, I, S) format. *E. coli and S. aureus* were categorised as susceptible or non-susceptible to the panel of antibiotics indicated for treatment of infections caused by the organisms.

Statistical Analysis

Categorical data were reported as percentage specimens stratified by level of hospital care (tertiary, regional, district). An overall chi square test was used to compare percentages of isolates susceptibility by hospital level for each antibiotic. If the overall chi-square was significant ($p < 0.05$), pairwise comparisons were explored. Where more than one comparison was significant, the most conservative p-value was reported

Kruskal-Wallis analysis of variance was used to compare average DDD per 1000 inhabitants by hospital level for each antibiotic. Overall significance was reported where the differences were not significant. Where significant, the overall p-value was not reported. Instead the Duncan multiple range test was used to test pairwise comparisons. Where multiple pairwise comparisons were significant, the most conservative p value was reported

Data was analysed using Stata v13 statistical software.

1.5 CHAPTER STRUCTURE

This research is presented in the following chapters:

- Chapter 1. The first chapter contains the introduction, literature review and a brief overview of the study design and methodology.
- Chapter 2. The second chapter consists of the manuscript entitled "Exploring trends between antibiotic use and resistance in public hospitals in the uMgungundlovu District" intended for publication in the South African Medical Journal.
- Chapter 3. The final chapter reflects on the extent to which the aim and objectives have been met, limitations are identified, recommendations are made and the significance of the study is presented.

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CHAPTER 2. MANUSCRIPT

The following manuscript intended for submission to the South African Medical Journal emanated from this study:

"Exploring trends in antibiotic use and resistance in public sector hospitals at different levels of healthcare in the uMgungundlovu District"

Contributions:

- Ms A. Desai, as the principle investigator, co-developed the study design, undertook the data capturing and data analysis, and, drafted the manuscript.
- Ms C. Connolly assisted with the statistical analysis.
- Professor F. Suleman, as co-supervisor, helped to design the study, facilitated data capturing and analysis, and contributed to the writing and revision of the manuscript.
- Professor SY Essack, as principle supervisor, co-designed the study, facilitated the analysis and contributed to the writing and critical review of the manuscript.

Exploring trends in antibiotic use and resistance in public sector hospitals at different levels of health care in the uMgungundlovu District

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Abstract

Background: Surveillance of antibiotic use and resistance plays an important role in identifying the drivers of antibiotic resistance. This study sought to identify trends and possible correlations between antibiotic use and resistance in three public sector hospitals at different levels of healthcare. Antibiotic use data was represented as defined daily doses (DDD)/1000 inhabitants and thereafter correlated with susceptibility data of antibiotics indicated for the treatment of *Escherichia coli and Staphylococcus aureus* as indicator Gram-negative and Gram-positive bacteria respectively.

Methods This was a retrospective, observational study conducted at three public healthcare facilities in the uMgungundlovu district. Data was obtained and analysed for the period 2014-2016. Provincial depot issuing data was used to calculate antibiotic consumption as defined daily doses/1000 inhabitants for each antibiotic, using World Health Organization (WHO) methodology. Antibiotic susceptibility data was obtained from the National Institute for Communicable Diseases (NICD) and was analysed based on susceptible and non-susceptible isolates for each antibiotic under investigation. Data was analysed using Stata v13 statistical software

Results There was a general trend of reduced antibiotic susceptibility as the levels of healthcare increased attributed to the fact that more severe and complex infections are treated at the higher levels of healthcare and require greater quantities of and/or broader spectrum antibiotics. For treatment of infections caused by *S. aureus* antibiotic use generally increased as the level of healthcare increased. Azithromycin was the most frequently used while linezolid was the least used antibiotic and showed the highest levels of susceptibility across all levels of healthcare. *S. aureus* showed the lowest level of susceptibility to cloxacillin across all the levels of healthcare and was indicative of the prevalence of methicillin-resistant *S. aureus* (MRSA). When antibiotic use was correlated with resistance, cloxacillin displayed a downward trend in use from 2014 to 2016 while cloxacillin resistance increased from 2014 to 2015 followed by a decrease in resistance in 2016 indicating that resistance is a function of time and use and that the lag time between the decrease in use and a corresponding decrease in resistance is not predictable and varies for different antibiotics in different healthcare settings. In contrast, azithromycin showed a steady decline in resistance although use increased over the three years (2014-2016). In the case of the treatment of infections caused by *E. coli* there was a general trend of the

greater use of narrow spectrum antibiotics at the lower district and regional levels while the broad-spectrum antibiotics were used more frequently at a tertiary level. Trimethoprim-sulphamethoxazole was used the most, whereas colistin was used the least. Contrary to expectations, there were higher susceptibility levels to third and fourth generation cephalosporins and meropenem at a tertiary level than regional level. *E. coli* showed lowest levels of susceptibility to ampicillin and highest level of susceptibility to levofloxacin across all levels of healthcare. When antibiotic use was correlated with resistance, antibiotics that were used frequently (sulphamethoxazole-trimethoprim, amoxicillin clavulanic acid and ampicillin) displayed high levels of resistance over the three years. Trimethoprim-sulphamethoxazole use decreased slightly over the year however resistance remained high. The same trend was observed with amoxicillin clavulanic acid and ampicillin use and resistance indicating possible co-selection of resistance by the use of other classes of antibiotics.
Conclusion This study added to the body of knowledge that there exists a link between the use of antibiotics and resistance, albeit not a direct causal one. Quantifying antibiotic use and identifying trends in resistance associated with antibiotic consumption assists prescribers and policy makers to improve antibiotic use, guide antibiotic stewardship programmes and optimise antibiotic policies and guidelines.

Keywords: *Escherichia coli*; *Staphylococcus aureus;* Defined Daily Doses; Antibiotic Consumption; Antibiotic Susceptibility; Antibiotic Resistance; Antibiotic Stewardship

Introduction

The advent of antibiotics in the 1920's has been pivotal in the treatment of bacterial infections. However, the indiscriminate use of antibiotics over the years has exerted selection pressure for the emergence of resistance that has reached unprecedented levels globally [1]. Two strategic objectives of the Global Action Plan (GAP) on Antimicrobial Resistance are (1) the surveillance of antibiotic use and resistance in order to identify the drivers of resistance and (2) evidence-based prescribing and dispensing to optimize antimicrobial use [2]. The vision of the South African Antimicrobial Resistance National Strategic Framework, 2014 – 2024 is "to ensure the appropriate use of antimicrobials by health care professionals in all health establishments in South Africa to conserve the efficacy of antimicrobials for the optimal management of infections and animal health" [3]. The framework draws attention to three main areas that contribute to improving the rational use of antibiotics and improving patient outcomes: (1) enhance infection prevention and control through vaccination programmes and improving water access and sanitation, (2) antibiotic stewardship interventions such as multi-disciplinary ward rounds and antibiotic prescription charts aimed at reducing unnecessary prescribing of antibiotics, and, (3) optimization of antibiotic surveillance which entails the monitoring of antibiotic use and resistance patterns[3].

Antibiotic use may be quantified as defined daily dose (DDD), which is "the assumed average maintenance dose per day for a drug used for its main indication in adults." It is a statistical tool used in medicine utilization research to improve medicine use. DDD is a fixed independent unit of measure that allows for the assessment of medicine trends and comparisons to be made internationally [4]. Antimicrobial consumption data represented as DDD can then be correlated with antibiotic susceptibility data to ascertain the drivers and trends in antibiotic use and resistance. This study explored the trends between antibiotics indicated for the treatment of *Escherichia coli* and *Staphylococcus aureus* in three public sector hospitals at different levels of healthcare, i.e. district, regional and tertiary in the uMgungundlovu district. Retrospective data on antibiotic use and resistance was analysed for the years 2014 – 2016/7 with antibiotic use correlated with antibiotic susceptibility for the selected isolates.

Methods

An observational, retrospective study was undertaken to quantify and analyse the relationship between antibiotic use and resistance. Data on antibiotic use and resistance was obtained for three hospitals at different levels of care (district, regional and tertiary) in the uMgungundlovu District over the study period of 2014-2016. The district provides a health service to 10% of the KwaZulu-Natal province which is an estimated 1 052 730 individuals [5].

Antibiotic Consumption data

Annual consumption data received from the Pharmaceutical Services Division of the KwaZulu-Natal Provincial Department of Health for the years 2014 to 2016 was filtered to find the data required for the antibiotics in question. This data was used to calculate DDD using the World Health Organization Collaborating Centre (WHOCC) for Drug Statistics Methodology consumption tool. Step-by-step guidelines provided by WHOCC on their website were used to accurately capture data on the electronic Antimicrobial Consumption (AMC) Tool which automatically calculated DDD once data was successfully entered [6]. Briefly, antibiotic consumption data in grams was converted into DDD. This is calculated by taking the total number of grams for each antibiotic and dividing it by number of grams per daily dose as indicated by WHO guidelines. DDD was adjusted to DDD per 1000 inhabitant days by taking DDD divided by total number of inhabitant multiplied by 365 days and then multiplying by 1000 [6]. The population denominator was chosen as (1) these three hospital form part of the referral system serving the total population of the uMgungundlovu district, (2) all three hospitals have a substantive out-patient population in addition to in-patients and (3) the susceptibility data was not stratified by out-patient and in-patient. (The potential limitations of this denominator choice are elaborated in the Discussion). The pathogens under investigation were *E. coli (*Gram-negative bacteria*)* and *S. aureus* (Gram-positive bacteria). The antibiotics that were selected to calculate DDD were therefore based on their indications for infections caused by the bacteria in question as recommended by the South African Antibiotic Stewardship Programme (SAASP) [7]. The antibiotic panel for *E. coli* was amikacin, amoxicillin/clavulanic acid, ampicillin,

cefepime, cefotaxime, ceftazidime, ceftriaxone, ciprofloxacin, colistin, gentamicin, imipenem, levofloxacin, meropenem, piperacillin/tazobactam, and trimethoprim sulphamethoxazole. The antibiotics selected for *S. aureus* were azithromycin, cloxacillin, clindamycin, linezolid and vancomycin.

Antibiotic Resistance

Susceptibility data for *E. coli* and *S. aureus* was obtained from the National Infectious Diseases Centre (NICD) for the years 2014 – 2017. *E. coli and S. aureus* were categorised as susceptible or non-susceptible to the panel of antibiotics in the resistant, intermediate, susceptible (R, I, S) format. . Percentage susceptibility was calculated.

Statistical Analysis

Categorical data were reported as per cent of specimens examined by hospital level of care (tertiary, regional, district). An overall chi square test was used to compare percentages of isolates susceptibility by hospital level for each antibiotic. If the overall chi-square was significant ($p < 0.05$), pairwise comparisons were explored. Where more than one comparison was significant, the most conservative p-value was reported

Kruskal-Wallis analysis of variance was used to compare average DDD per 1000 inhabitants by hospital level for each antibiotic. Overall significance was reported where the differences were not significant. Where significant, the overall p-value was not reported. Instead the Duncan multiple range test was used to test pairwise comparisons. Where multiple pairwise comparisons were significant, the most conservative p value was reported

Data was analysed using Stata v13 statistical software.

Results

Table I shows antibiotic consumption for the antibiotics selected based on their indication for infections caused by *S. aureus* presented as the mean DDD per 1000 inhabitants for the different levels of hospital-based health care (2014-2016).

Table I. Antibiotic consumption based on their indication for infections caused by *S. aureus* presented as the mean DDD per 1000 inhabitants for the different levels of hospital-based health care (2014-2016)

	Hospital level						
	District	Regional	Tertiary		Pairwise Comparison‡		
Antibiotic	Mean*	Mean *	Mean*	p-value†	District vs. Regional	District vs. Tertiary	Regional vs. Tertiary
Azithromycin	0.058	0.110	0.015	0.03	0.09	0.09	0.004
Clindamycin	0.000	0.006	0.011	0.04	0.07	0.006	0.1
Cloxacillin	0.010	0.032	0.019	0.1	-	-	-
Linezolid	0.000	0.001	0.000	0.07	-	-	-
Vancomycin	0.000	0.002	0.008	0.03	0.09	0.004	0.09

* DDD per 1 000 inhabitants

† Chi-square test

‡ If p-value was <0.05 a pairwise comparison made between two of the participating hospitals at different levels of healthcare

Azithromycin, clindamycin and vancomycin were the three antibiotics to which a statistically significant (p<0, 05) difference in use was observed between the different levels of care. Pairwise comparison revealed a statistically significant difference in azithromycin use between regional and tertiary hospitals where use was greater at regional level. Pairwise comparisons also showed statistically significant differences in clindamycin and vancomycin use between district and tertiary levels with greater use at tertiary level. Azithromycin was most frequently used. Vancomycin was not used at district level and its use at regional and tertiary level for the 3 years was minimal.

There were a total of 121 525 isolates from the three participating hospitals over the period 2014-16, amongst which were 24 579 *S. aureus* isolates and 96 946 *E. coli* isolates.

Table II shows antibiotic susceptibility (%) for each antibiotic based on their indication for infections caused by *S. aureus* for different levels of hospital-based health care (2014-2016)

Table II. Antibiotic susceptibility (%) for each antibiotic based on their indication for infections caused by *S. aureus* for the different levels of hospital-based health care (2014-2016)

	Hospital level						
	District	Regional	Tertiary		Pairwise		
Antibiotic	%	%	%	p-value†	District vs. Regional	District vs. Tertiary	Regional vs. Tertiary
Azithromycin	87.9	88.2	80.8	<0.001	0.9	0.007	<0.001
Clindamycin	90.1	87.9	79.1	<0.001	0.3	<0.001	<0.001
Cloxacillin	88.8	88.0	77.8	<0.001	0.7	<0.001	<0.001
Linezolid	100	100	100	-	-	-	-
Vancomycin	100	99.9	99.8	0.5	-	-	-

A general trend of decreased susceptibility with higher levels of healthcare was observed. The susceptibility of *S. aureus* to azithromycin susceptibility was significantly lower at tertiary level than at district and regional levels and showed the lowest susceptibility compared to other antibiotics. Clindamycin susceptibility decreased as the level of care increased. Cloxacillin resistance ranged between 11, 2% to 22, 2% indicative of 11, 2% and 22, 2% methicillin-resistant *S. aureus* (MRSA) at district and tertiary levels respectively. Vancomycin-resistant *S. aureus* (VRSA) appeared to be emerging at regional and tertiary levels but linezolid retained full (100%) susceptibility at all levels.

Table III shows antibiotic consumption for the antibiotics selected based on their indication for infections caused by *E. coli* presented as mean DDD per 1000 inhabitants for different levels of hospital-based health care (2014 – 2016).

Table III. Antibiotic consumption based on their indication for infections caused by *E. coli* presented as mean DDD per 1000 inhabitants for different levels of hospital-based health care (2014 – 2016)

	Hospital level						
	District	Regional	Tertiary		Pairwise		
Antibiotic	Mean*	Mean *	Mean*	p-value†	District vs. Regional	District vs. Tertiary	Regional vs. Tertiary
Amikacin	0.000009	0.0009	0.005	0.051	-	-	-
Amoxicillin/ clavulanic acid	0.020	0.078	0.036	0.04	0.01	0.1	0.07
Ampicillin	0.013	0.047	0.015	0.07	-	-	-
Cefepime	0.00005	0.0001	0.0002	0.04	0.06	0.01	0.1
Cefotaxime	0.00002	0.001	0.000	0.03	0.004	0.09	0.09
Ceftazidime	0	0.0002	0.001	0.03	0.09	0.003	0.09
Ceftriaxone	0.020	0.047	0.009	0.03	0.09	0.09	0.004
Ciprofloxacin	0.041	0.067	0.056	0.4	-	-	-
Colistin	0	0.0002	0.0001	0.06	-	-	-
Gentamicin	0.0035	0.020	0.013	0.051	-	-	-
Imipenem	0	0.012	0.024	0.051	-	-	-
Levofloxacin	0	0.0005	0.0010	0.04	0.06	0.005	0.1
Meropenem	0	0.002	0.003	0.04	0.06	0.005	0.1
Piperacillin/ Tazobactam	0.00001	0.018	0.018	0.07	-	-	-
Trimethoprim sulphamethoxazole	0.443	1.009	0.341	0.2	-	-	-

* DDD per 1 000 inhabitants

† Chi-square test

There was a general trend of greater use of narrower spectrum antibiotics at regional level (e.g. ampicillin, amoxicillin-clavulanic acid and trimethoprim-sulphamethoxazole) while broader spectrum antibiotics were more frequently used at the higher tertiary level of care (e.g. amikacin, ceftazidime, cefepime, imipenem, meropenem and levofloxacin). Statistically significant differences in use were

evident for amoxicillin/clavulanic acid, all third and fourth generation cephalosporins, meropenem and levofloxacin mainly between district and regional and/or tertiary levels. Only ceftriaxone showed a significant difference in use between regional and tertiary levels of care. Trimethoprim-sulphamethoxazole was the most frequently used antibiotic at all levels of care with no statistical significance across the levels of health care followed by amoxicillin/ clavulanic acid and ampicillin. Carbapenem, colistin and piperacillin/tazobactam use was minimal.

Table IV shows antibiotic susceptibility (%) for each antibiotic based on their indication for infections caused by *E. coli* for different levels of hospital-based health care (2014-2017).

Table IV. Antibiotic susceptibility (%) for each antibiotic based on their indication for infections caused by *S. aureus* for different levels of hospital-based health care (2014 – 2016)

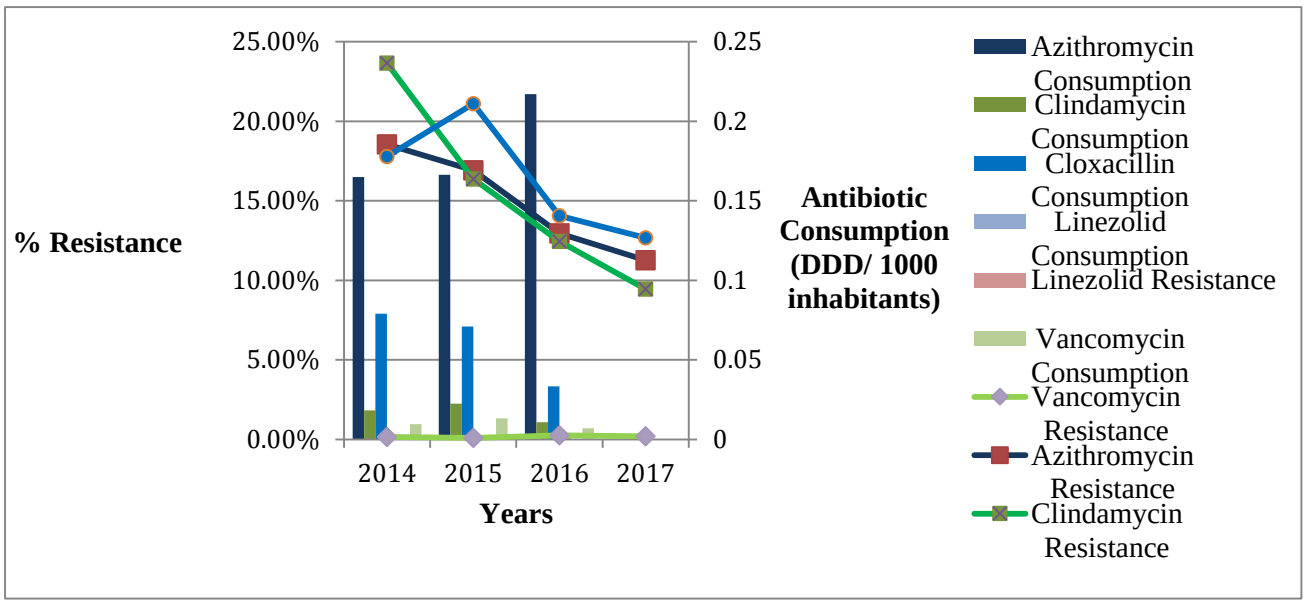
	Hospital level						
	District	Regional	Tertiary		Pairwise comparison		
Antibiotic	%	%	%	p-value†	District vs. Regional	District vs. Tertiary	Regional vs. Tertiary
Amikacin	92.9	95.2	93.9	0.07	-	-	-
Amoxicillin clavulanic acid	56.8	60.7	56.3	0.003	0.3	0.9	0.001
Ampicillin	16.2	16.6	15.8	0.7	-	-	-
Cefepime	72.0	78.3	72.6	<0.001	0.046	0.9	<0.001
Cefotaxime/ Ceftriaxone	70.3	80.0	72.8	<0.001	0.001	0.46	<0.001
Ceftazidime	72.5	80.7	72.8	<0.001	0.007	0.9	<0.001
Ciprofloxacin	69.7	78.7	64.6	<0.001	0.004	0.2	<0.001
Colistin	97.8	99.6	99.5	0.002	-	-	-

Gentamicin	78.1	87.9	81.9	<0.001	-	-	-
Imipenem	100	99.7	99.5	0.2	-	-	-
Levofloxacin	100	-	100	-	-	-	-
Meropenem	97.8	99.8	99.4	<0.001	<0.001	0.01	0.006
Piperacillin/ Tazobactam	77.1	82.7	78.3	<0.001	0.057	0.7	<0.001
Trimethoprim Sulphamethoxazole	28.0	25.2	26.9	0.3	-	-	-

Statistically significant differences in susceptibility of *E. coli* to amoxicillin-clavulanic acid, the third and fourth generation cephalosporins and ciprofloxacin were evident between regional and tertiary levels with lower susceptibility in the latter. A similar trend was observed for the third and fourth generation cephalosporins and meropenem between district and regional levels of care with lower susceptibility observed in the former, contrary to expectations. This contradiction was also observed for meropenem between the district and tertiary levels of care with lower susceptibility again at district level. *E. coli* showed the lowest level of susceptibility to ampicillin, ranging between 15% -16% across all three hospitals, followed by trimethoprim-sulphamethoxazole ranging from 25,2-28% and amoxicillin-clavulanic acid ranging from 56,3-60,7%. Although use of carbapenems, colistin and piperacillin/tazobactam was minimal, resistance was present; ranging between 17, 3% - 22, 9% across the three hospitals. Piperacillin/ tazobactam susceptibility was significantly lower at tertiary level compared to regional level and there was no significant difference between district and tertiary levels.

Figure I graphically portrayed the trend between antibiotic consumption and resistance for all three hospitals with regards to treatment of infections caused by *S. aureus*.

Figure I showing combined yearly antibiotic consumption and resistance trends

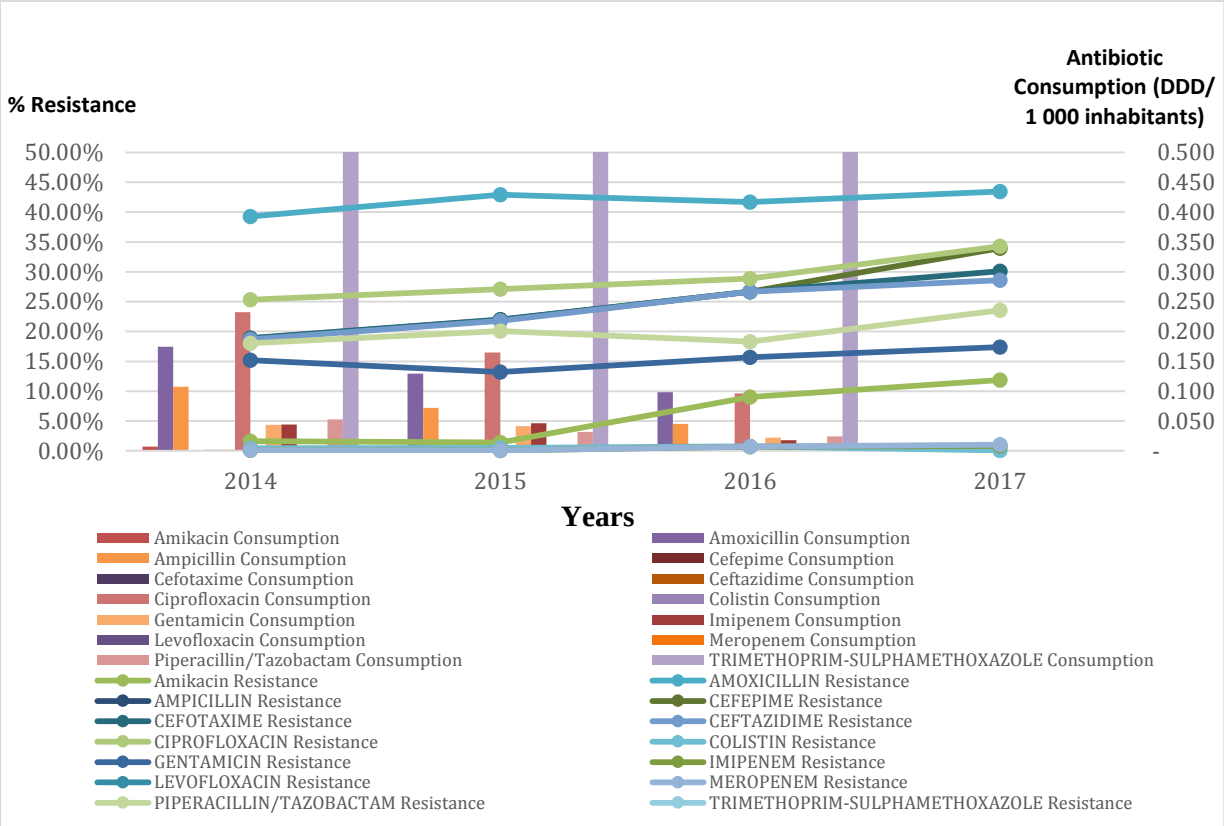


for all three hospitals implicated in the treatment of *S. aureus*

Cloxacillin displayed a trend where resistance increased from 2014 to 2015 and when antibiotic usage decreased in 2016 so did resistance. There was a decrease in resistance to clindamycin over the years. Vancomycin use increased from 2014 to 2015 and decreased thereafter in 2016 with resistance remaining minimal. Azithromycin consumption increased over the three years but there was a steady decline in resistance.

Figure II graphically portrayed the trend between antibiotic consumption and resistance for all three hospitals with regards to treatment of infections caused by *E. coli*.

Figure II showing combined yearly antibiotic consumption and resistance trends for all three hospitals implicated in the treatment of Escherichia coli



Trimethoprim-sulphamethoxazole and ampicillin consumption decreased over the three years but resistance levels remained high. There was a slight decrease in amoxicillin resistance in 2016 with a decrease in amoxicillin consumption between 2015 and 2016. Although ciprofloxacin usage decreased over the three years there was a steady increase in ciprofloxacin resistance.

Discussion

This study explored the trends in antibiotic use (calculated as DDD/1000 inhabitants) and susceptibility patterns in a Gram-negative organism (*E. coli*) and a Gram-positive organism (*S. aureus*) at different levels of healthcare in a single district in KwaZulu-Natal, South Africa. Data from all three hospitals were further aggregated and correlations between antibiotic use consumption and resistance were explored in an

effort to ascertain the impact (if any) of selective pressure on the emergence of antibiotic resistance.

Three general trends were evident: (1) there was greater use of narrower spectrum antibiotics at the lower district and regional levels while broader spectrum antibiotics were more frequently used at the higher tertiary level of care, (2) decreased antibiotic susceptibility was evident at higher levels of healthcare and (3) there was no direct causal relationship between antibiotic use and resistance.

General trends (1) and (2) re-iterate the principle behind the healthcare referral system of South Africa. Patients are referred to a district hospital if adequate treatment is not available from a primary healthcare level. If further complex treatment is required patients are to be referred from a district to a regional hospital. If the regional hospital does not have the requisite services, then the patient is referred from a regional to a tertiary hospital where diagnostic procedures and treatment of a specialized nature is provided [8]. Conditions that are more severe that require the use of broad-spectrum antibiotics are used at the higher levels of healthcare. The third trend speaks to the co-selection of resistance and the role infection prevention and control. Co-selection refers to resistance to more than one antibiotic due to a genetic linkage of the resistant genes. The use of one antibiotic could result in resistance to that as well as other classes of antibiotics whose resistance genes are co-carried on the same piece of DNA usually on mobile genetic elements such as plasmids, transposons and integrons [9]. Therefore, a direct relationship between the use of a single antibiotic or antibiotic class and the emergence of resistance is difficult to prove. Moreover, a confounding factor is the transfer of infections is through contact between within and between patients and healthcare workers [10]. There is the increasing need for reinforcing hand hygiene and maintaining good hospital cleaning practices, staff education, improved communication and antibiotic stewardship interventions to uphold a favourable infection control standard within hospitals [11].

When antibiotic consumption and resistance was compared by hospital level it was evident that azithromycin was used most frequently and was associated with the lowest susceptibility of all the antibiotics tested against *S. aureus* albeit ranging between 80, 8% and 88, 2% (Table I). The same trend was found with trimethoprim-

sulphamethoxazole, ampicillin and amoxicillin/clavulanic acid use and resistance. This supports the theory that although the relationship between antibiotic use and resistance is not a causal one, there is a link between selection pressure of antibiotic use and the emergence of resistance [12-14]. Antibiotic use of vancomycin, colistin, carbapenems (meropenem and imipenem) and piperacillin/tazobactam displayed increase in use as the level of care increased. This is in accordance with the referral system where broader spectrum antibiotics are used at higher levels of care in treating more complex conditions [14]. The 100% susceptibility of linezolid in all three hospitals and vancomycin at the district hospital is welcomed and hopefully will be maintained (Table II). It is important to reserve these antibiotics for the treatment of severe infections where no alternative treatment is available.

According to SAASP guidelines for methicillin susceptible *S. aureus* (MSSA) cloxacillin, clindamycin, ceftriaxone and amoxicillin clavulanic acid are the antibiotics of choice [7]. Resistance to cloxacillin and clindamycin already range between 10%-22.2% (Table II). It is important to work on interventions to prevent further resistance to these antibiotics. For MRSA vancomycin is indicated, as the antibiotic of choice and clindamycin and moxifloxacin should only be prescribed if sensitivity results have been obtained. Bearing this in mind the high susceptibility levels of vancomycin need to be retained.

According to SAASP guidelines, the recommended first line treatment of *E. coli* is ceftriaxone, amoxicillin/clavulanic acid, ciprofloxacin and aminoglycosides (gentamicin, amikacin etc.). The choice of antibiotic is dependent on the type of infection. Ampicillin is not recommended as an antibiotic of choice due to frequent resistance and poor clinical outcome and trimethoprim-sulphamethoxazole should only be used when sensitivity results have been obtained [[7]. The high level of resistance to ampicillin and trimethoprim-sulphamethoxazole was evident in our study across all levels of care. It is important to incorporate these guidelines into hospital antibiotic policies, standard treatment guidelines and associated national essential medicines lists, and to notify prescribers of the recommended first line therapy for infections caused by the bacteria in question. This is to assist in reducing the indiscriminate use of antibiotics and the subsequent emergence and spread of resistance.

There is a plethora of studies exploring and examining the link between antibiotic use and resistance. The correlation is not a direct one. For example when yearly trends between antibiotic consumption and resistance were investigated, ciprofloxacin consumption had decreased over the study period however resistance to the antibiotic had increased over the years. This could be attributable to confounding factors which include and are not limited to infection prevention and control measures, invasive procedures in the hospital setting, patient history, disease profile and timely administration of antibiotics by nursing staff [15]. Confounding factors were not included in this study and proved to be a limitation. Reduction in resistance also varies across bacteria. Rate of resistance is associated with the way in which resistance is developed either through *de novo* mutation or acquired resistance (Horizontal Gene Transfer (HGT) of resistant determinants) [9]. Therefore trying to correlate antibiotic use and resistance on a yearly basis proved to be complex. A direct causal relationship between antibiotic use and resistance was not achieved. On-going surveillance at hospitals need to be established. This will assist in having updated hospital records on antibiotic use and resistance within the facility. Data can be presented to hospital management, policy makers and prescribers to make them aware of the current antibiotic consumption and resistance statistics of the facility. If possible, reduction of unnecessary antibiotic prescribing should be achieved without compromising patient outcomes.

The main limitation of the study in terms of denominator data was that information on patient numbers provided with antibiotics was not available. This is a result of sub-optimal information systems in the public sector. Moreover, patient record databases in the public sector are not electronically captured necessitating the use of catchment population data as the denominator (DDD/1 000 inhabitants). The use of DDD/1 000 inhabitants allows one to assume in and out patient consumption, however, this may be an underestimation of use. Bed occupancy (DDD/100 bed days) is an estimate of inpatient consumption only and could therefore result in overestimation.

Selective pressure is a concern when it comes to the emergence of resistance and steps should be taken to reduce the indiscriminate use of antibiotics.

Conclusion

This study compared antibiotic use and susceptibility at three levels of hospital care. In most cases, a trend of highest antibiotic susceptibility was found on a district level then regional and followed lastly by tertiary. This is in line with the healthcare referral system in South Africa. The association between antibiotic selection pressures resulting in resistance is well documented and results from this study added to the body of knowledge that it is not a direct causal relationship. As recommended in the South African Antimicrobial Resistance Framework objectives there is the need for on-going surveillance that will assist in creating a database for monitoring and evaluation of antibiotic consumption and its impact on the emergence and or changes to antibiotic resistance. Such a database will additionally allow the early detection of outbreaks. Moreover, the dissemination of surveillance data to prescribers and policy makers will assist in improving antibiotic prescribing, provide evidence based antibiotic stewardship interventions and improve on current antibiotic guidelines tailored for hospitals based on their specific antibiotic consumption and susceptibility profiles.

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CHAPTER 3. CONCLUSION

3.1 Introduction

Antibiotic consumption data for three hospitals at different levels of care were successfully converted into DDD/ 1000 inhabitants to express antibiotic consumption according to WHO recommendations. Antibiotic resistance data was presented as percentage susceptibility. Comparisons on antibiotic use and resistance were made between the different levels of health care (i.e. district, regional and tertiary). Yearly antibiotic consumption was correlated with yearly susceptibility trends to demonstrate the relationship between antibiotic use and resistance.

The following were the main conclusions:

- There was greater use (DDD/ 1000 inhabitants) of narrower spectrum antibiotics at the lower district and regional levels while broader spectrum antibiotics were more frequently used at the higher tertiary level of care.
- Decreased antibiotic susceptibility was evident at higher levels of healthcare.
- When yearly antibiotic consumption (DDD/1000 inhabitants) was correlated with antibiotic resistance patterns for both *E. coli and S. aureus*, antibiotics that were used frequently displayed higher resistance levels, however, a direct causal relationship could not be established
- There is the need for on-going surveillance to create a database to generate an evidence base for interventions such as antibiotic guidelines based on hospital specific antibiotic use and susceptibility profiles.

3.2 Limitations

- To calculate DDD annual consumption depot data received from Provincial Department of Health for the years 2014 to 2016 was used. By using depot data, one is unable to determine whether the medication was in actual fact prescribed and/or administered.
- Using catchment population data (DDD/1000 inhabitants) as a denominator resulted in a possible underestimation of antibiotic consumption.
- There was no information available on the patients who received the antibiotics used. DDD gives us a quantitative idea regarding antibiotic use but no indication of the

quality of prescribing or whether the prescribed antibiotic was actually taken by the patient. DDD is a technical measurement to represent antibiotic use it does not necessarily reflect the recommended or average prescribed dose.

- Confounding factors (i.e. infection prevention and control, invasive procedures in the hospital setting, patient history, disease profile and timely administration of antibiotics by nursing staff) do play a role in the emergence of resistance; however, they were not taken into account in this study.

3.3 Recommendations

The following recommendations are made based on the results of this study:

- DDD should be used in the public sector across facilities to monitor antibiotic consumption as it allows for standardised comparisons to be made between institutions, nationally and internationally.
- Monitoring sensitivity profiles in hospitals will assist in updating and improving hospital specific antibiotic guidelines.
- Alternative denominators for quantification for example days of therapy (DOT) for each antibiotic should be explored. DOT provides a sum of days in which each antibiotic was administered. Length of therapy (LOT) – also known as antibiotic exposure time is the number of days that the patient received an antibiotic irrespective of the number of different antibiotics. Both DOT and LOT are measures for reporting antibiotic use using patient level data.
- A study design that takes into consideration confounding factors that affect the emergence of resistance should be developed.

3.4 Significance

The WHO Antimicrobial Consumption (AMC) tool had been successfully used to calculate DDDs. This tool can be used in the hospital and community setting to capture antibiotic consumption as DDDs in order to monitor antibiotic stewardship programmes and to assess the impact of interventions aimed at reducing antibiotic consumption. By using WHO methodology to calculate antibiotic consumption it allows for comparisons to be made both nationally and internationally. Exploring trends between antibiotic consumption and susceptibility patterns showed, that to a certain extent, the relationship between antibiotic use and resistance can be correlated, bearing in mind that a direct causal relationship cannot be

deduced as there are confounding factors including but not limited to different levels of care, infection and prevention control and patient and disease profiles.