THE IMPACT OF ANTIMICROBIAL STEWARDSHIP ON ANTIBIOTIC USE – A RETROSPECTIVE REVIEW IN A PRIVATE HOSPITAL, JOHANNESBURG, GAUTENG

A mini-dissertation submitted by

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DECLARATION

I, Aisha Mahomeddi, declare that the dissertation hereby submitted to the Sefako Makgatho Health Sciences University, for the degree of Masters in Pharmacy (MPharm), in the School of Pharmacy, has not previously been submitted by me for a degree at this or any other university; that it is my work in design and execution, and that all material contained herein has been duly acknowledged.

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Mahomeddi, A (Miss)
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LIST OF ABBREVIATIONS

AMR- Antimicrobial Resistance
AMS– Antimicrobial Stewardship
BJI- Bone and Joint Infection
BSI- Bloodstream Infection
CDDEP- Center for Disease Dynamics Economics and Policy
CDI- *Clostridium difficile* Infection
CNS- Central nervous system
CVS- Cardiovascular system
DDD- Defined Daily Dose
NDOH- National Department of Health
DOT- Days of Therapy
EENT- Ear, Eye, Nose and Throat
ESBL- Extended spectrum beta-lactamases
FIDSSA- Federation of Infectious Diseases Society of Southern Africa
GARP- Global Antimicrobial Resistance Partnership
GIT- Gastro-intestinal tract
ICU - Intensive Care Unit
IDSA- Infectious Diseases Society of America
LRTI- Lower respiratory tract infection
MRSA- Methicillin resistant *Staphylococcus aureus*
SAASP- South African Antibiotic Stewardship Programme
U.S- United States of America
WHO- World Health Organization
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Abstract

The impact of antimicrobial stewardship on antibiotic use - a retrospective review in a private hospital in Johannesburg, Gauteng.

Introduction

Antimicrobial resistance has become a global threat and requires a dedicated universal approach to prevent the lapse into a post-antibiotic era. For decades, the consumption of antimicrobials in medicine, veterinary science, agriculture and poultry has proceeded unchecked. One method to address antimicrobial resistance is the implementation of AMS programmes in healthcare settings (Davey, et al., 2013).

An AMS programme was implemented recently at the study site and this study aims to determine if antibiotic stewardship has an impact on defined daily dose (DDD), days of therapy (DOT), *Clostridium difficile* infection (CDI) rates and cost of antibiotics in an intensive care unit (ICU) and medical ward of a private hospital.

Method

This study compared antibiotic use, DDD, and *Clostridium difficile* infection (CDI) rate for patients admitted to the ICU and medical ward of the study site between January - June 2013, which was the control group, and January - June 2015, which was the study group.

Data was obtained retrospectively from computer records at the study site. Each patient that met the inclusion criteria for both the control period (January - June 2013) and the study period (January - June 2015) were entered into this review. Antibiotic type, number of days of antibiotic therapy, cost of antibiotic therapy, DDD data and CDI rate were compared between the two groups.

Results

There was a non-significant decrease in DDD per 100 bed days from the control group to the study group of 1.36 (p=0.8169). The DDD per 100 bed days decreased in the ICU by 3.71 and increased with 1 in the medical wards. The DOT decreased by 0.15 and this was not statistically significant (p-value= 0.5485). For the ICU, the DOT increased by 0.12 days and for the medical ward, the DOT decreased by 0.28 days.
The reduction in CDI rate between the control group and the study group was not statistically significant (p=0.1417). The cost of therapy increased during the study period. The total increase in cost per patient was R743.61. The cost per patient in the ICU increased by 28.3% and the cost per patient in the medical ward increased by 10.9%.

**Conclusion**

The implementation of an AMS programme in a private hospital setting did not result in a significant decrease in the DDD, DOT and CDI rate, and resulted in an increase in the cost of antimicrobial therapy. It can be seen from this study that implementing an AMS programme does not guarantee a decrease in DDD, DOT, CDI rate and antimicrobial cost.
CHAPTER ONE

INTRODUCTION

This introductory chapter describes the background and rationale for this study. The research question is provided; followed by the aim and objectives. The importance of conducting this study is described. An outline of the chapters of the dissertation concludes this chapter.

1.1 Problem statement and rationale for the study

An AMS programme was implemented at the study site, a 128-bed private hospital situated in Johannesburg, South Africa, in May 2014, until currently. The programme was started by the ward/AMS pharmacist working together with hospital and pharmacy management to form a structured AMS committee comprising of the relevant healthcare disciplines, such as a physician chairperson and advisor, AMS pharmacist, hospital manager, nursing manager, ward unit managers, and microbiologists for each of the three laboratories which service the study site.

Historically, the first-described AMS programme was in the early 1970s, when Boston City Hospital showed that restricting use of selected antibacterial agents could have a marked impact on patterns of antibacterial use (Goff, 2015; McGowen and Finland, 1974; Rybak, 2015).

Currently, very few studies on the impact of the AMS programme in private hospitals in South Africa have been conducted. It is therefore important to determine if implementation of an AMS programme has resulted in a decrease in the consumption of antimicrobials. This can be measured by comparing antimicrobial defined daily dose (DDD) rates, expenditure on antimicrobials, rate of Clostridium difficile infection and duration of antibiotic therapy before and after an AMS programme was implemented in order to determine if the programme was effective.

1.2 Research question

Does antibiotic stewardship have an impact on defined daily dose (DDD), days of therapy (DOT), Clostridium difficile infection (CDI) rates and cost of antibiotics in an intensive care unit (ICU) and medical ward of a private hospital?
1.3 Purpose of the study

1.3.1 Aim of the study

This study aimed to determine if an AMS programme implemented in the ICU and medical wards of a private hospital in Gauteng had any impact on outcome measures as defined by: defined daily dose (DDD), days of therapy (DOT), *Clostridium difficile* infection (CDI) rate and cost of antibiotics (direct medicine costs using antibiotic utilisation/consumption).

1.3.2 Objectives of the study

The objectives of this retrospective study were as follows:

- To evaluate baseline data of current antibiotic prescribing patterns against measures such as DDD, days of therapy, CDI rate and cost of antibiotics
- To conduct a post-implementation audit after stewardship had been implemented and to assess the following measures: DDD, days of therapy, CDI rate and cost of antibiotics
- To measure the effectiveness of antibiotic stewardship by evaluating if there has been a change in the following measures: DDD, days of therapy, CDI-rate and cost of antibiotics, as the aim of antibiotic stewardship is to curb the inappropriate use of antibiotics, thereby reducing the incidence of antibiotic resistance.

1.4 Importance of the study

Antimicrobial resistance has become a global threat and requires a dedicated universal approach to prevent the lapse into a post-antibiotic era. For decades, the consumption of antimicrobials in medicine, veterinary science, agriculture and poultry has proceeded unchecked. The drug development pipeline for new antibiotics shows very little promise, therefore other methods to preserve antimicrobials currently in use must be implemented. One such method is the implementation of AMS programmes in healthcare settings (Davey, *et al.*, 2013).

Currently, there is limited data and studies evaluating the effectiveness of antimicrobial stewardship interventions. More studies are needed to assist in furthering the development and improvement of AMS programmes and initiatives. Therefore, this study was created to evaluate the impact of an AMS programme on specific outcome measures, such as DDD, CDI rate and cost of antibiotics.
1.5 Outline of the study

Chapter 1 introduces the reader to the study and this includes the problem statement and the rationale for the study. The aim and objectives of the study were laid out thereafter. Chapter 2 includes the literature review and studies that have been conducted that will assist with the research question concerning this study. Chapter 3 provides a detailed description of the methodology of the study. Chapter 4 contains the results and discussion of the study. Chapter 5 is a summary of the results and conclusion.
CHAPTER TWO

LITERATURE REVIEW

2.1 Introduction

In this chapter, the literature pertaining to the study is reviewed. The topics that were explored in the literature review include the definition of antimicrobial stewardship (AMS); the need for antimicrobial stewardship; AMS locally and internationally; the overuse of antimicrobial agents; AMS programmes and policies; AMS teams; AMS measures and the role of the pharmacist in AMS.

2.2 Definition of antimicrobial stewardship

The term antimicrobial stewardship (AMS) was initially conceived in 1997 as “a collection of strategies, policies, guidelines or tools that could improve antimicrobial prescribing with the aim of decreasing antimicrobial resistance (AMR) and use” (Howard et al., 2014). This definition varies from country to country, as well as the priorities, policies, guidelines, impact and outcomes.

Antibiotics are pharmaceutical agents that either inhibit or destroy bacterial growth (Jetacar, 1999). The World Health Organisation (WHO) views antimicrobial agents as a global public good (one that is non-excludable and non-rival in consumption) (Mendelson and Matsoso, 2015). Programmes, policies and interventions that reduce the inappropriate use of antimicrobials; slow down the development of antimicrobial resistance; improve patient outcomes and reduce costs associated with prolonged antimicrobial use can be considered as part of antimicrobial stewardship. Although AMS programmes may differ, they all share a common aim.

2.3 The need for antimicrobial stewardship

Due to antimicrobial resistance, the effectiveness of antibiotics that are being used to treat infections has been steadily declining, and with the detection of multi-drug resistant bacteria, pan-drug resistant bacteria, and extreme drug resistant bacteria in humans, we are fast-approaching a post-antibiotic era (Center for Disease Dynamics, Economics and Policy, 2013). Antimicrobial resistance has been described as one of the major threats to individual and population health in the 21st century, and national and international organisations have repeatedly underlined the urgent need for action (Davies and Gibbens, 2013; O’Neill, 2014).
The Center for Disease Dynamics, Economics and Policy published a report in September 2015 regarding the state of the world’s antibiotics, explaining that the effectiveness of antibiotics has been decreasing globally, and requesting strong antibiotic stewardship to reduce antibiotic overuse in humans.

Antimicrobial resistance is a Darwinian response to selective pressure due to the antimicrobial agent, however, the principle cause for resistance is overuse of antimicrobial agents (Mendelson, 2014). Resistance occurs by bacterial mutation due to antibiotic exposure that results in a competitive advantage for the mutated strains. There are various strategies used by bacteria to resist the effects of antibiotics, such as mutation of antimicrobial targets; active efflux of antimicrobial agents; biofilm production preventing antimicrobial entry and the creation of bypasses that allow the bacteria to function without using the enzymes that are targeted by antimicrobial agents (Penesyan et al., 2015). These resistant genes are found on chromosomal as well as transmissible extrachromosomal elements (Laxminarayan et al., 2013). Due to international travel, these resistant strains are circulated globally.

In South Africa, 52% of 1147 viable *Staphylococcus aureus* isolates taken from ICU patients were found to be methicillin-resistant *Staphylococcus aureus* (MRSA) (Laxminarayan et al., 2013). New Delhi metallo-beta lactamase -1 (NDM-1) was first found in September 2011 in South Africa. At various sites in South Africa, 72% of *Klebsiella pneumoniae* isolates from July 2010 - August 2011 were suggestive of extended spectrum beta-lactamases (ESBL) production (Laxminarayan et al., 2013).

According to a report in 2013 commissioned by the Lancet Infectious Diseases Journal on antibiotic resistance and the need for global solutions, the high rates of antibiotic use in high-income countries has contributed to selection pressure giving rise to drug-resistant strains of bacteria and resulting in the use of broader-spectrum antibiotics (Laxminarayan et al., 2013). Antibiotic use was also noted to be increasing in low-and-middle income countries, as the rate of antibiotic resistance infections increased (Laxminarayan et al., 2013).

In 2014, the UK government suggested that by 2050, AMR could result in a $100 trillion financial loss and a death toll of 300 million people (O’Neill, 2014). Similarly, the Centers for Disease Control and Prevention in the USA estimate that AMR results in healthcare costs of $20 billion and the US economy experiences a $35 billion loss in productivity each year. (Center for Disease Control and Prevention, 2013).
2.4 AMS internationally and locally

In 2014, results of an international cross-sectional survey of AMS programmes in 660 hospitals across 67 countries in Africa, Asia, Europe, North, South and Central America and Oceania found that 58% of hospitals had an antimicrobial stewardship programme. Of these hospitals, only 62% had a formal AMS committee; 46% had a policy or procedure for antimicrobial stewardship; 38% published a yearly report on AMS and 29% had a published work plan (Howard et al., 2014). Developed countries exhibited a more consistent approach to AMS than developing countries (Howard et al., 2014). Europe exhibited the highest AMS standards in the hospital setting, and Africa had the lowest, due to AMS being in its infancy in this region.

The World Health Assembly approved the Global Action Plan on Antimicrobial Resistance in May 2015, which requires countries to implement the strategies within two years (WHO, 2015). The US has implemented a National Action Plan for Combating Antibiotic-Resistant Bacteria and the European Commission has also implemented a similar plan (European surveillance-antimicrobial consumption, 2011). The Center for Disease Dynamics, Economics and Policy (CDDEP) has created a global antibiotic resistance map to monitor the progress of antimicrobial stewardship globally (CDDEP, 2015).

In response to the World Health Organization (WHO) Global Antibiotic Resistance Partnership (GARP), GARP-SA identified an urgent need for AMS and the South African Antimicrobial Stewardship Programme (SAASP) was formed as a part of the Federation of Infectious Diseases Societies of Southern Africa (FIDSSA). This involved both the public and private healthcare sectors in the country forming AMS teams using the required skills of microbiologist, infectious diseases specialists, physicians, pharmacists, infection control practitioners, nursing staff and key healthcare stakeholders. The objectives of these programmes are “to promote appropriate antibiotic prescribing, education and engagement with (and in support of) the National Department of Health, as the effector arm of the ABR (antibiotic resistance) response”. Advocacy by SAASP coupled with encouragement from the WHO for Member States to develop a national plan to combat antimicrobial resistance (AMR), has resulted in the development of the national strategy framework for AMR (Mendelson and Matsoso, 2015).

A recent study published in the Lancet Infectious Diseases Journal in June 2016 evaluating AMS across 47 South African hospitals using a prospective audit and feedback strategy between October 2009 and September 2014 found that the AMS programme resulted in a significant reduction in DDD’s (Brink et al., 2016).
AMS was implemented by the private hospital group to which the study site belongs at many of their hospitals. The AMS programme comprises of a pharmacist-initiated prospective audit and review of the following: antibiotic hang-time; antibiotic therapy without culture results; redundant duplicate coverage; concurrent use of four or more antimicrobials; duration of antimicrobial therapy greater than seven or fourteen days and the correct use of antimicrobials that require a loading dose (Messina et al., 2015).

These interventions were implemented at the study site to decrease the inappropriate use of antimicrobial agents. However, the interventions are not measured in this study, as the study focuses on specific outcome measures that indicate if antibiotic usage has changed. The AMS pharmacist at the study site was responsible for the prospective audit and review of all patients on antimicrobials in the ICU and medical ward at the study site. Feedback and/or recommendations were provided to the relevant clinician, who then chose to either accept or reject the recommendation.

2.5 Overuse of antimicrobial agents

Alexander Fleming warned us about AMR during his Nobel lecture in 1945. During the past decade, the understanding of antibiotics as a limited and invaluable resource has resulted in a radical change in the perception of antibiotic use, as well as the consequences of over-prescribing of these agents (Fleming, 1945).

Antibiotic misuse has become a major global public health concern, as it is associated with the development of antimicrobial resistance, adverse effects, increased costs, and increased length of hospital stay (Tenover, 2006). Due to increasing numbers of multi-drug resistant bacteria and the lack of novel antimicrobial drug development, one of the solutions currently being advocated is the rational use of antimicrobial agents as well as discouraging the use of antimicrobials for illnesses that are self-limiting, and for viral infections (Weber, 2005). Since the year 2000, increasing rates of resistance in bacteria such as Pseudomonas aeruginosa, Acinetobacter baumannii and Klebsiella pneumoniae to third-generation cephalosporins and quinolones in the ICU setting has been observed (Ntagiopoulos et al., 2007).

The overuse of antimicrobial agents can result in the emergence of resistance and an increase in healthcare costs and length of hospital stay (Bantar et al., 2003). The misuse of antimicrobials has been described internationally in both private and public healthcare facilities and emphasise the need for policies that govern the use of this limited resource (Chung et al.,
An additional concern is the recent findings that the use of antibiotics in critically ill patients without bacterial infection can increase mortality (Hranjec et al., 2012).

South Africa has been highlighted recently as a major contributor to the increase in global antibiotic use (Van Boeckel et al., 2014). Findings from a study in South Africa evaluating prescribing patterns in the ICU indicate that a number of factors play a role in the development of AMR, but antibiotic prescribing was found to be one of the most important factors (Chunnilall et al., 2015).

Of all the medicines available for use in humans globally, antibiotics are one of the most familiar and most often used, and the resulting decline in efficacy of these agents is not of great concern to the individual or the prescriber as resistance affects the next patient, and this fosters greater antibiotic overuse and resistance (CDDEP, 2015). However, it is important to note that every individual will be affected by AMR if we do not halt the progression of resistance (Littmann, 2015).

2.6 AMS programmes and policies

Various international medical professional organisations such as the WHO and the Infectious Diseases Society of America (IDSA), the ESCMID Study Group for Antibiotic Policies (ESGAP), as well as local professional organisations such as the Federation of Infectious Diseases Societies of Southern Africa (FIDSSA) and the Global Antibiotic Resistance Partnership (GARP) and the National Department of Health in South Africa have formulated policies and standards for AMS.

The IDSA and the Society for Healthcare Epidemiology of America have developed guidelines for developing an institutional programme to enhance antimicrobial stewardship. The core strategies as advocated by this guideline is prospective audit with intervention and feedback, formulary restriction and pre-authorisation. Other stewardship strategies discussed in this guideline include education, guidelines and clinical pathways, antimicrobial cycling, combination therapy, streamlining or de-escalation therapy, dose optimisation, conversion from parenteral to oral therapy, clinical microbiology and computer surveillance and decision support (Dellit et al., 2007).

The IDSA guideline for AMS advocating prospective audit with intervention and feedback is utilized at the study site. Formulary restriction and pre-authorisation is not utilized at the study site, as there are no infectious diseases specialists present to assist with the implementation
of such strategies. The AMS pharmacist at the study site is responsible for conducting a prospective audit with intervention and feedback for all patients on antibiotics in the ICU and medical ward.

The aim of AMS programmes is to reduce the use and misuse of antimicrobial drugs by optimizing the initiation, selection, dosing, route of administration and duration of therapy and thereby limit the increase of AMR, *Clostridium difficile* infection and adverse drug events (Dellit, et al., 2007). Various American and European infectious diseases societies have created guidelines for institutional antimicrobial stewardship programmes (Gould, 2001).

### 2.7 Antimicrobial stewardship teams

As per the IDSA guideline on developing an antimicrobial stewardship programme, team members of an AMS team should include an infectious diseases physician; a clinical pharmacist with infectious diseases training, an information system specialist; an infection control practitioner, a clinical microbiologist and a hospital epidemiologist. This programme is usually directed by the infectious diseases physician or by the clinical pharmacist with infectious diseases training together with the infectious diseases physician (Dellit *et al.*, 2007). In resource-limited countries such as South Africa, AMS teams typically comprise of a pharmacist (with or without clinical knowledge and/or infectious diseases training), a physician or other clinician (with or without infectious diseases training), microbiologist and infection prevention practitioner.

### 2.8 Antimicrobial measures

AMS programmes can be evaluated to see if the aim of the programme has been met, however, at present there is no standardized set of outcomes that need to be met (Chung, *et al.*, 2013). Antibiotic consumption is often used as a benchmark for AMS programmes, as ecological evidence links antibiotic use with antibiotic resistance (Goossens, 2009).

AMS programmes primarily measure antimicrobial use antibiotic consumption, days of therapy and costs with each measure having its advantages and disadvantages. Additional measures such as clinical outcomes, morbidity and mortality, length of stay, by incidence of *Clostridium difficile* and resistance patterns are also tools to determine the usefulness of such programmes, however, certain parameters are often difficult to measure. Measurement should not be focused on determining if the data meets a certain target or cost-savings threshold, but should aid us in determining if changes implemented as a result of an AMS programme are effective (Nathwani, *et al.*, 2011).
Consumption measures are often reported as utilisation per 1000-patient-days. The dispensing system is normally utilised for this information, though the most accurate measure is administered drug. Many programmes do not have the resources to determine the defined daily dose (DDD) per drug administered (Madaras-Kelly, 2003).

2.8.1 Defined daily dose

Defined daily dose (DDD) is a measure that was developed in the 1970's and has been modified by the WHO for drug statistics methodology. It is “the average maintenance dose per day for a drug used for its main indication in adults” (WHO, 2013). For example, if the DDD for amoxicillin is 1500mg, the drug usage (DDD) can be calculated by multiplying the number of amoxicillin issued by the amount of amoxicillin in each capsule issued, divided by the given DDD of 1500mg. Therefore, if a patient received 3 amoxicillin capsules, and each capsule contained 500mg amoxicillin, the DDD for this patient’s amoxicillin is 1.

This measure was not created to be used for measurement of AMS impact and has many drawbacks. Firstly, the DDD measurement underestimates antibiotic use in patients with renal failure. Secondly, total antibiotic use in a hospital to calculate DDD includes antibiotics administered to paediatric patients, for which the DDD methodology does not apply. Thirdly, where the administered dose is significantly higher or lower than the WHO DDD for a specific antimicrobial agent, the DDD will be a false reflection of the number of days of therapy. However, due to a lack of better measures it is widely used by hospitals both locally and internationally and allows for comparison with other institutions, by standardising the DDD data per 1000 patient-days (Polk et al., 2007). For this study, DDD is expressed per 100-patient days. The WHO currently recommends normalizing consumption to 100-patient days.

Expressing DDD per patient days results in a standardised format and allows for benchmarking between hospitals, regions, and even countries. Most hospitals in the U.S report consumption by DDDs per 1000-patient days, as recommended by IDSA. The creation of standardised DDD methodology has been a huge advantage in allowing comparisons between institutions (Polk et. al., 2007).

2.8.2 Days of therapy

Days of Therapy (DOT) is defined as the number of days that a patient receives an antimicrobial agent, regardless of the dose. If a patient is receiving more than one antimicrobial agent on the same day, the final DOT for this patient will be the sum of the DOT for each antibiotic. DOT can be standardised to 1000-patient days for comparison between other
hospitals. DOT favours monotherapy over combination therapy. Antimicrobial DOT is a more relevant measure of AMS programmes as it requires observing actual administration of the drug, but most hospitals are unable to calculate days of therapy, making it a less common outcome measure in AMS programmes (Polk, et al., 2007).

2.8.3 Costs of therapy

Antimicrobial costs can be a measure of purchasing, dispensing or administration of antibiotics over a specified time period. Purchasing and dispensing costs can only provide an estimate of antimicrobial consumption, as this does not take into account unused medication returned back to the pharmacy for credit (Bantar et al., 2003) Another method of comparing cost of therapy can be the use of antimicrobial costs as a function of patient-days of care, using hospital census data (Nowak et al., 2012).

Antimicrobial expenditure costs also take into account the cost of antimicrobials for the entire hospital and cannot retrieve costs for specific wards. At the study site, it was not possible to retrieve the pharmacy budget allocated for antimicrobials, or the amount of the pharmacy budget spent on antimicrobials per ward. Therefore, for this study, antimicrobial costs were calculated per patient, per antimicrobial, for both the control group and the study group, using fixed acquisition costs.

2.8.4 Incidence of *Clostridium difficile* infection

Treatment with antibiotics results in an unbalance of the intestinal microflora, due to the antibiotic destroying large numbers of bacteria that are part of the normal intestinal flora. This can result in the overgrowth of *Clostridium difficile*. *Clostridium difficile* infection can result in significant costs, increased length of hospital stay and can prove fatal in at-risk patient populations, such as the elderly, patients with multiple comorbidities and the immunocompromised patients (CDDEP, 2015). The number of *Clostridium difficile* infection (CDI) per 1000-patient days can be used as a measure of the effectiveness of the AMS programme, as *Clostridium difficile* infection can be the result of collateral damage caused by prescribing antimicrobial agents (Davey et al., 2013). CDI rate can be expressed as the number of newly diagnosed CDI cases per 1000 patient admissions. It is calculated by the number of newly acquired CDI cases, divided by the number of inpatient days for that specific time period, multiplied by 1000.

Good infection control measures together with an effective antimicrobial stewardship programme have resulted in a decline in hospital-acquired *Clostridium difficile* infections
(Feazel et al., 2014). In a study conducted at a tertiary-care hospital in South Africa, the annual incidence of *Clostridium difficile* infection (both community and hospital-acquired) was 8.7 cases per 10 000 admissions (Rajabally et al., 2013).

### 2.8.5 Incidence of multi-drug resistant infections

This measure looks at the number of patients with a specific drug-resistant organism divided by the total number of patients admitted to the ward or facility within a specified time-frame (Morris et al., 2012). This measure enables us to quantify resistance and monitor trends over time, and can also be an indicator of the effectiveness of the AMS and infection control programmes. Changes in resistance patterns lag behind changes in antibiotic consumption therefore this measure should be evaluated over extended periods of time. The incidence of multi-drug resistant infections measure requires microbiology resources to monitor susceptibility data. These resources were not available at the study site therefore this measure could not be utilised for the study.

### 2.8.6 Hospital-associated antibiotic resistant organism infection rate

This measure looks at the number of new hospital-acquired infections such as methicillin resistant *Staphylococcus aureus* (MRSA) or vancomycin resistant *Enterococcus* (VRE) per 1,000 patient days and can be used to assess the efficacy of the AMS and infection control programmes.

### 2.9 The role of the pharmacist in AMS

The role of the pharmacist in AMS programmes has been clearly defined by The American Society of Health-System Pharmacists (ASHP, 2010) and can be described as follows:

i. Ensuring that the indication, drug, dose, route and duration for prescribed antibiotics is optimised to prevent or minimise the incidence of resistance and adverse antibiotic-related events.

ii. Participating in the formulation of guidelines, protocols and standards for optimising AMS.

iii. Education of healthcare providers, staff members, patients and family, as well as the community in general on infection prevention and protecting antimicrobial agents as a limited resource.
iv. Organising and leading the multi-disciplinary AMS programme at a facility-level to ensure that policies are created and implemented that optimise antimicrobial use and prevent overuse and misuse of these agents.

v. Collecting, compiling and analysing data pertaining to antimicrobial use, antimicrobial costs, length of hospital stay, rates of AMR, rates of compliance to AMS guidelines and policies as well as assessing outcomes of the AMS programme.

vi. Publication and sharing of AMS outcomes and programmes on a local and international level.

vii. Working together as a team on multi-disciplinary ward rounds involving microbiologists, physicians, intensivists, surgeons, infection control practitioners and nursing staff to ensure judicial antimicrobial use and better patient outcomes.

viii. Actively participating in the infection control programme and collaborating on AMS and infection control projects.

ix. Utilising technology and social media to enhance AMS spread and improve the quality and ease of data collection and analysis.

x. Ensuring the correct storage, dispensing, labelling, mixing and administration of antimicrobial agents.

In 2014, the WHO required that all nations develop a strategy to combat antimicrobial resistance that is in alignment with GARP. South Africa developed the Antimicrobial Resistance National Strategic Framework (South African Department of Health, 2015) consisting of five key strategic objectives:

i. Interdisciplinary governance structures

ii. Diagnostic stewardship – improving the use of diagnostic tools to identify infections better

iii. Optimise surveillance and early detection of antimicrobial resistance

iv. Enhance infection prevention and control of the spread of resistant microbes to patients in healthcare settings

v. Promote appropriate use of antimicrobials in human and animal health through antimicrobial stewardship

The key enablers of the above objectives are: legislative policy and reform; education; communication and research.
2.10 AMS activities/ interventions at the study site

AMS activities in this study focused on the following parameters:

- De-escalation interventions based on culture results and clinical response
- Intervention made by AMS pharmacist if antimicrobial therapy was commenced without cultures being taken
- Daily ward rounds to evaluate patients receiving antimicrobial therapy and prospective feedback (verbal, email, mobile text message or note on patients chart) to the clinician if the pharmacist made any recommendations or interventions
- Excessive duration of antimicrobial therapy was monitored for antibiotics exceeding 7 days and 14 days of therapy and interventions to stop excessive therapy were recommended by the AMS pharmacist where required
- IV to oral switch was recommended where possible
- Dosing of antimicrobial drugs was optimised by the AMS pharmacist to prevent the development of resistance due to suboptimal doses, as well as to prevent patient toxicity with high doses
- Surgical prophylaxis was monitored to ensure that prophylaxis did not extend beyond 24 hours post operatively and also to ensure that the appropriate antibiotic was administered as surgical prophylaxis
- At the study site, antimicrobial stewardship activities and interventions are only undertaken during working hours of a regular 45 hour work week and not after hours or during the weekend. If a patient’s therapy can be changed to a narrower spectrum or stopped during the weekends or after the work day has ended, this intervention is not made until working hours.

These AMS activities were not measured in this study. Rather, quantitative outcomes based on antimicrobial consumption was utilised to determine the effectiveness of the AMS programme.
Antimicrobial resistance is a universal, complex and multi-faceted problem, requiring a solution that targets all the factors that contribute to the development and spread of resistance. This chapter has explored the need for AMS, the reasons for development of resistance, the global coverage of AMS, policies and strategies of AMS and various measures of AMS programmes. This study aimed to determine if an AMS programme implemented in the ICU and medical wards of a private hospital in Gauteng has any impact on DDD, DOT, CDI-rate and antibiotic costs.
CHAPTER THREE

METHOD

3.1 Introduction

This chapter describes the methodology used to conduct the study. The chapter starts with the purpose of the study, a description of the study site, a description of the study design, a description of the study period and the study population. The pilot study that was conducted prior to the data collection is followed by an explanation of the sample selection. The data collection instruments are individually discussed after which the data capturing and analysis procedures are outlined. Measures to ensure reliability and validity of data are provided followed by the ethical considerations for this study, which concludes the chapter.

3.2 Purpose of the study

The purpose of the study was to evaluate the impact of an AMS programme on DDD, DOT, CDI rate and cost of antibiotic therapy.

3.3 Study site

The study was done in the ICU and medical ward in a private hospital situated in Johannesburg, South Africa. The ICU is operated as a closed unit with 10 beds. A closed unit means that there are dedicated medical staff in the unit who attend to the patients unlike an open unit where any medical doctor can admit and attend to a patient in the unit. There are 36 beds in the medical ward. The ICU and medical wards were chosen for the study as these are the wards with the highest antimicrobial consumption at the study site and therefore the wards with the highest AMS activity.

3.4 Study design

A retrospective, case-control and descriptive research design was followed by reviewing patient records with measurable quantitative aspects such as DDD, CDI rate, days of antibiotic therapy and cost of antibiotic expenditure.

Actual antimicrobial stewardship interventions conducted by the AMS pharmacist daily, on a Monday to Friday, during work hours, were not measured as part of the study, as the outcomes of these interventions on antibiotic use was measured.
3.5 Study Period

This study compared data from January - June 2013 (control group) with data from January - June 2015 (study group). The AMS programme was implemented in May 2014.

3.6 Study population and sample selection

Only patients that required and received antibiotics for ≥ 2 days (48 hours) in the medical ward and ICU were included in the study.

3.7 Data collection

As this study is a retrospective record review, data such as patient age, gender, admission diagnosis, name of antibiotic/s administered, ICD-10 code/s and days of antibiotic therapy were extracted from the SAP (Systems, Applications and Products) dispensing system, the Bluebird® AMS system and the admission registers for the respective ward by the AMS pharmacist.

1. Patients that met the inclusion criteria at the study site had their medication record reviewed from January 2013 - June 2013 (control group) and January 2015 - June 2015 (study group).

2. Data for both the study group and the control group was recorded on the data collection sheet (Appendix 1)

3. DDD and antibiotic expenditure data was extracted from monthly data reports and recorded on the collection sheet for DDD data

4. DOT was extracted from the data collection sheet. If a patient received more than one antibiotic, both antibiotics were counted separately.

5. CDI rate was extracted from monthly poke yoke data for 2013 and Bluebird® infection control data for 2015. The monthly poke yoke is a data collection tool utilised by the private hospital group for infection control and prevention. This tool tracks a number of factors, such as the incidence of hospital-acquired infections, *Clostridium difficile* infection, surgical site infections, and multi-drug resistant infections. The CDI rate was calculated by the number of patients newly diagnosed with hospital-acquired CDI, divided by the number of inpatient days for that time period, multiplied by 1000.

6. Cost data was calculated per patient for every antimicrobial. This was calculated by taking the antibiotic used; the number of units used per day; the number of days of therapy and the cost per unit to obtain a total cost of therapy for each antimicrobial for each patient.
Both the control group and the study group utilized 2013 cost of antimicrobial data to ensure that the two groups could be compared. The daily antibiotic cost per patient was calculated by the multiplication of unit price and number of daily doses that was used for that infection. The total cost per patient for both the control group and the study group was then added and an average cost per patient per group was obtained to determine if the implementation of an AMS programme resulted in cost savings.

3.8 Data collection instruments

A data collection form (Appendix 1) was utilised to collect the data. The data collection form was designed specifically for this study. No changes were made to the data collection form following the pilot study. The following data was collected for each patient being studied:

1. Patient number
2. Patient age
3. Patient gender
4. Name of antibiotic/s administered
5. Number of days of antibiotic therapy
6. Primary diagnosis for antibiotic therapy

3.9 Data capture and analysis

Data was extracted retrospectively from SAP and Bluebird® for both the study group and the control group. DDD data is captured at head office from billings data and was extracted from monthly reports.

SAP is a hospital dispensing, billing and stock management system. It records patients’ data such as age, gender, admission dates, transfer dates, discharge dates as well as all medication dispensed.

Bluebird® is an AMS application which allows one to track and record all antibiotic related data for patients admitted to the hospital.

The data was captured onto a spread sheet for interpretation and analysis. This report provided information and statistics regarding patient demographics, antibiotics used, number of days of antibiotic therapy, ward that the patient was admitted to, ICD-10 code for primary diagnosis, DDD data per ward, and CDI rate for both the study and control period.
Demographic details of patients were summarised descriptively by frequency tables and graphs. Frequency tables were constructed for type/s of antibiotics administered. All statistical procedures were performed on SAS (SAS Institute Inc., Cary, NC, USA), Release 9.4, BM running under Microsoft Windows on a personal computer.

3.10 Statistical considerations

3.10.1 Sample size:

No formal sample size estimation was done. As this was a retrospective review study, antibiotic use was compared before (2013) and after (2015) the introduction of an AMS programme. Patients treated during 2013, before the introduction of the programme, were considered the control group and patients treated during 2015, after the introduction of the programme, were considered the study group.

3.10.2 Sampling procedure:

Data was extracted retrospectively from SAP and Bluebird® for both the study group and the control group. DDD data was captured at head office from billings data, and extracted from monthly reports.

No specific sampling procedure was used. Due to the retrospective nature of this study, all patients that met the inclusion criteria for the study period and the control period were included.

3.10.3 Statistical analysis:

The data was captured into a Microsoft Excel™ 2013 edition spreadsheet.

Data was analysed with the assistance of a statistician. All statistical procedures were performed on SAS (SAS Institute Inc., Cary, NC, USA), Release 9.4, running under Microsoft Windows for a personal computer. The statistical analysis comprised a comparison of the test group with the control group in respect of the antimicrobial measures discussed in chapter 2, section 2.8.

Continuous variables such as age and duration of therapy were summarised by mean, standard deviation, median, interquartile range, minimum and maximum values. Categorical variables such as gender were summarised by frequency counts and percentage calculations.

Data from the control group was compared to data from the study group to determine if there was any difference in DDD, DOT, CDI rate and cost of antibiotic therapy.
3.11 Pilot study

A pilot study was conducted using the data collection instrument in Appendix 1 on 10 patients from the hospital's neurological rehabilitation ward. The data collection was designed specifically for this study.

As this data collection sheet (Appendix 1 and 2) has never been applied in practice before, a pilot test was performed to assess validity and reliability. The purpose was to ensure that the data collection sheet was sufficient and contained all aspects that needed to be addressed in the study. By performing a pilot test on the data collection sheet any shortcomings, mistakes, unnecessary or insufficient aspects were highlighted. No changes were made to the data collection form following the pilot study.

The pilot study was done after approval and certification by Sefako Makgatho Health Sciences Research and Ethics committee (SMUREC) had been received.

3.12 Reliability and validity of data

3.12.1 Reliability

Reliability refers to the consistency of a measure (Gravetter and Forzano, 2011). Utilising the data collection sheet after completing the pilot test ensured reliability. The data was collected and entered onto the data collection sheet by the investigator, and this was double checked by a second person for consistency and reliability.

3.12.2 Validity

Validity refers to whether the study is able to scientifically answer the questions it is intended to answer (Gravetter et al., 2011). Validity was ensured by the use of a pilot tested data collection sheet.

3.13 Bias

Bias was limited by sampling procedure, as all patients that met the inclusion criteria during the control period and the study period were included in the study.

3.14 Ethical considerations

Ethical approval was obtained from the Sefako Makgatho Health Sciences University (Approval number: SMUREC/H/71/2016: PG. see Appendix 4)
Approval to conduct research was obtained from the private hospital groups’ ethics and research committee. (Approval Number: UNIV 2016-0028- see Appendix 5)

3.15 Summary

In this chapter, the methods and instruments used to collect and record the data were discussed. The methods and procedures discussed were the study design; the study site; the study population; the study period; pilot study; sample selection, data collection and data collection instruments; data entry and analysis; the reliability, validity and bias. Finally, the chapter ended with the ethical aspects of the study.

The results obtained in the study and the discussion follows in Chapter 4.
CHAPTER 4

RESULTS AND DISCUSSION

4.1 Introduction

The results and discussion will be presented in this chapter. The chapter starts with a brief discussion of the patient demographics, such as the gender and age distribution and comparison to similar studies. Factors such as the diagnosis for the control group and study group, per ward and the type of antimicrobials prescribed are discussed thereafter, and compared with current literature. This is followed by a discussion of the results according to the objectives of the study: the defined daily dose results, the CDI rate, the days of therapy results and the cost of therapy for the control group and study group, as well as comparisons to similar studies for these objectives.

4.1.1 Patient demographics

A total of 681 patient files were reviewed for this study. The control group comprised of 254 patients (52 ICU patients and 202 medical ward patients). The study group comprised of 427 patients (156 ICU patients and 271 medical ward patients). There was an increase in patient admissions during the study period.

Two wards were utilized for the study, the ICU and medical ward, as these are the wards with the highest antimicrobial consumption at the study site; therefore, the bulk of the AMS pharmacists’ time was spent in these wards.

4.1.2 Gender and age

For 2015, Statistics South Africa (Stats SA) estimates the mid-year population as 54.96 million people. Approximately 51% (approximately 28.07 million people) of the population is female. The study population comprised of 43.9 % (n=681) males and 56.1% (n=681) females (refer to Table 4.1.1). There were more females than males for this study in both the ICU and the medical ward (refer to Table 4.1.2 and Table 4.1.3, respectively), and this is representative of the South African population according to Statistics South Africa. The gender ratio is similar to other antimicrobial stewardship studies (Katsios et al., 2012; Marchaim et al., 2012).

Approximately 30.2% of the population in South Africa is aged younger than 15 years and approximately 8.0% (4, 42 million) is 60 years or older (Stats SA). The mean age for the study
group was 62.6 years and the mean age for the control group was 64.9 years (refer to Table 4.1.1). This is older than the mean age for similar studies, but is representative of the mean age of patients seen at this hospital (Katsios et al., 2012; Marchaim et al., 2012). The medical ward patients for both the control group and the study group were younger than the ICU patients.

Table 4.1.1: Gender and age for both groups

<table>
<thead>
<tr>
<th>Population</th>
<th>% Male</th>
<th>% Female</th>
<th>Mean Age (yrs.) (Std. Dev)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Group (n = 254)</td>
<td>42.5</td>
<td>57.48</td>
<td>64.9 (±19.6)</td>
</tr>
<tr>
<td>Study Group (n = 427)</td>
<td>44.7</td>
<td>55.27</td>
<td>62.6 (±18.7)</td>
</tr>
</tbody>
</table>

Table 4.1.2: Gender and age for the ICU

<table>
<thead>
<tr>
<th>Population</th>
<th>% Male</th>
<th>% Female</th>
<th>Mean Age (yrs.) (Std. Dev)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Group (n = 52)</td>
<td>36.5</td>
<td>63.5</td>
<td>73.9 (±16.0)</td>
</tr>
<tr>
<td>Study Group (n = 156)</td>
<td>57.7</td>
<td>42.3</td>
<td>68.8 (±16.8)</td>
</tr>
</tbody>
</table>

Table 4.1.3: Gender and age for the Medical ward:

<table>
<thead>
<tr>
<th>Population</th>
<th>% Male</th>
<th>% Female</th>
<th>Mean Age (yrs.) (Std. Dev)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Group (n = 202)</td>
<td>44.1</td>
<td>56.0</td>
<td>62.6 (±19.8)</td>
</tr>
<tr>
<td>Study Group (n = 271)</td>
<td>37.3</td>
<td>62.7</td>
<td>59.0(±18.8)</td>
</tr>
</tbody>
</table>

4.2 Diagnosis

The most common diagnosis for the control group as well as the study group was pneumonia. This was a similar finding in other antimicrobial stewardship studies (Morel et al., 2010; Lesprit et al., 2009). The top five most common infection diagnosis for the control group was pneumonia (75%); urinary tract infections (UTI) (34%); gastro-intestinal infections (GIT) (32%); skin and soft tissue infections (SSTI) (26%); and unspecified infections (15%) (refer to Figure...
In comparison, the top five most common infection diagnosis for the study group was pneumonia (25%); systemic infection (16%); lower respiratory tract infections (LRTI) (10%); urinary tract infections (UTI) (10%) and unspecified infections (9.8%) (refer to Figure 4.2.4). The total is more than 100% as patients could have had more than one infection.

For the ICU, the incidence of pneumonia, gastro-intestinal infections and urinary tract infections decreased during the study period (refer to Figure 4.2.1). However, the incidence of lower respiratory tract infections, systemic infections and unspecified infections increased during the study period. The incidence of skin and soft tissue infections remained relatively stable throughout the control and study period. The incidence of bone and joint infection, bloodstream infection and cardiovascular system infection cannot be compared, as they were not present for both the control and the study period.

For the medical ward, the incidence of bone and joint infections, bloodstream infections, central nervous system infections, pneumonia and skin and soft tissue infections decreased during the study period (refer to Figure 4.2.2). However, the incidence of lower respiratory infections, systemic infections and unspecified infections increased during the study period.
The incidence of ear, eye, nose and throat infections, gastro-intestinal infections and urinary tract infections remained relatively stable throughout the control and study period.

The differences between bloodstream infections and systemic infections during the study period may be due to infections being labeled as systemic if the organism was cultured from two or more sources, for example, blood culture and urine culture. Therefore, the rate of bloodstream infections during the study period declined, however the rate of systemic infections increased.

Similarly, the rate of pneumonia declined during the study period, however the rate of lower respiratory tract infections increased, and this may be due to the diagnosis of pneumonia only being applied during the study period by the AMS pharmacist if the patient met the criteria for pneumonia (chest radiography, the criterion standard for establishing the diagnosis of pneumonia). If the patient did not meet the criteria for pneumonia, the diagnosis of lower respiratory tract infection was applied.

There is a large difference in the diagnosis of pneumonia between the control group and the study group. During the control period, no AMS programme existed, and the patients’ diagnosis was recorded in the patient file by the nurse assigned to that patient on the day of admission. Should the initial diagnosis prove to be incorrect, it was often not corrected in the patients file. In contrast to this, during the study period, when an AMS programme was implemented, the patients’ infection diagnosis was recorded on the Bluebird AMS application by the ward pharmacist and updated as soon as the diagnosis was changed. Therefore, the incidence of pneumonia in the control group may have been overestimated in comparison to the study group.
Notes: BJI: bone and joint infection; BSI: bloodstream infection; CNS: central nervous system infection; CVS: cardiovascular system infection; EENT: ear, eye, nose or throat infection; GIT: gastro-intestinal system infection; LRTI: lower respiratory tract infection; SSTI: skin and soft tissue infection; Systemic infection: positive culture results from 2 or more sites with infection source unknown; Unspecified: Infectious diagnosis not specified; UTI: urinary tract infection.

Figure 4.2.2: Diagnosis in the medical ward (n=473)

Notes: BJI: bone and joint infection; BSI: bloodstream infection; CNS: central nervous system infection; CVS: cardiovascular system infection; EENT: ear, eye, nose or throat infection; GIT: gastro-intestinal system infection; LRTI: lower respiratory tract infection; SSTI: skin and soft tissue infection; Systemic infection: positive culture results from 2 or more sites with infection source unknown; Unspecified: Infectious diagnosis not specified; UTI: urinary tract infection.

Figure 4.2.3: Diagnosis for control group (n=254)
4.3 Antimicrobials prescribed

A wide range of antibiotics were utilized by both the control group as well as the study group. The antibiotics used in both the control and study groups were penicillin and enzyme inhibitors, macrolides, carbapenems, antipseudomonal penicillins, cephalosporins and glycopeptides. Amoxicillin-clavulanate was the most commonly prescribed antimicrobial for both the control group and the study group (refer to Table 4.3.1).

The top five most commonly prescribed antimicrobials for the control group were: amoxicillin-clavulanate (15.8%); ceftriaxone (8.7%); metronidazole (8.7%); ciprofloxacin (7.5%); meropenem (6.3%) and piperacillin-tazobactam (6.3%). In comparison, the top five most commonly prescribed antimicrobials for the study group were: amoxicillin-clavulanate (18%); clarithromycin (10.5%); ertapenem (9.1%); piperacillin-tazobactam (7%) and cefuroxime (6.6%).

The study group had a significant increase in the use of ertapenem (3.62%). The control group did not have any patients on colistin but the study group did (0.7%). Oral vancomycin use in the control group was not specified, therefore it is difficult to compare this with the study group. There was an increase in the use of linezolid in the study group (1.5%). The control group did
not use any trimethoprim sulfamethoxazole but the study group did (2.34%) (Refer to Table 4.3.1).

Table 4.3.1: Antimicrobials prescribed for the control group (n=254) and study group (n=427)

<table>
<thead>
<tr>
<th>Name of Antibiotic</th>
<th>Indication (G+, G-, anaerobe)</th>
<th>Control group (%)</th>
<th>Study group %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>G-</td>
<td>2</td>
<td>0.2</td>
</tr>
<tr>
<td>Amoxicillin-clavulanate</td>
<td>G+,G-, anaerobe</td>
<td>15.8</td>
<td>18.3</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>G+</td>
<td>0.8</td>
<td>0.2</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>atypical G+</td>
<td>3.2</td>
<td>4.7</td>
</tr>
<tr>
<td>Benzyl penicillin</td>
<td>G+</td>
<td>0.4</td>
<td>0</td>
</tr>
<tr>
<td>Cefepime</td>
<td>G+ and G-</td>
<td>3.9</td>
<td>4.2</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>G-</td>
<td>0.4</td>
<td>0</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>G- plus strep</td>
<td>0</td>
<td>0.2</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>G-</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>G- plus strep</td>
<td>8.7</td>
<td>3</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>G+ and G-</td>
<td>4.3</td>
<td>6.6</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>G-</td>
<td>7.5</td>
<td>5.2</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Atypical G+</td>
<td>4.7</td>
<td>10.5</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>G+</td>
<td>0</td>
<td>0.7</td>
</tr>
<tr>
<td>Cloxacillin</td>
<td>G+</td>
<td>2.8</td>
<td>2.6</td>
</tr>
<tr>
<td>Colistin</td>
<td>G-</td>
<td>0</td>
<td>0.7</td>
</tr>
<tr>
<td>Doripenem</td>
<td>G+,G-, anaerobe</td>
<td>0.4</td>
<td>0.9</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>G+</td>
<td>0.8</td>
<td>0.5</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>G+,G-, anaerobe</td>
<td>5.5</td>
<td>9.1</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>G+</td>
<td>0.8</td>
<td>0.2</td>
</tr>
<tr>
<td>Imipenem-cilastatin</td>
<td>G+,G-, anaerobe</td>
<td>1.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>G-</td>
<td>0</td>
<td>0.2</td>
</tr>
<tr>
<td>Linezolid</td>
<td>G+</td>
<td>3.2</td>
<td>4.7</td>
</tr>
<tr>
<td>Meropenem</td>
<td>G+,G-, anaerobe</td>
<td>6.3</td>
<td>4.5</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Anaerobe</td>
<td>8.7</td>
<td>5.4</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>G+ and G-</td>
<td>4.3</td>
<td>3</td>
</tr>
<tr>
<td>Phenoxy methyl penicillin</td>
<td>G+</td>
<td>0.4</td>
<td>0</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>G+, G-, anaerobe</td>
<td>6.3</td>
<td>7</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>G+</td>
<td>2</td>
<td>1.6</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>G+</td>
<td>3.5</td>
<td>1.4</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>G+,G-, anaerobe</td>
<td>0</td>
<td>0.7</td>
</tr>
<tr>
<td>Trimethoprim-</td>
<td>G+</td>
<td>0</td>
<td>2.3</td>
</tr>
<tr>
<td>sulfamethoxazole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin oral</td>
<td>G+</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>Vancomycin IV</td>
<td>G+</td>
<td>2</td>
<td>0.2</td>
</tr>
</tbody>
</table>
In comparison to the control group, the study group reflects a decrease in the prescription of anaerobe cover; a decrease in the prescription of Gram-positive cover and a decrease in the prescription of Gram-negative cover. There was an increase in the prescription of atypical Gram-positive cover and an increase the prescription of broad spectrum cover (Gram-positive and Gram-negative, as well as Gram-positive, Gram-negative and anaerobe) (refer to Figures 4.3.1 and 4.3.2). The increase in broad spectrum cover and atypical Gram-positive cover reflects the trend towards broader empiric therapy until the infectious organism is identified.

Figure 4.3.1: Percentage of antimicrobials prescribed for control group by spectrum of cover (n=254)

Figure 4.3.2: Percentage of antimicrobials prescribed for study group by spectrum of cover (n=427)
For the ICU, the use of amoxicillin-clavulanate, cefepime, meropenem, metronidazole, piperacillin-tazobactam and teicoplanin decreased during the study period. The use of clarithromycin, ertapenem, linezolid and trimethoprim-sulfamethoxazole increased during the study period (refer to Figure 4.3.3). Similarly, a study in the U.S investigating the impact of regular collaboration between infectious diseases and critical care practitioners on antimicrobial use found that significant reductions were observed in the use of extended-spectrum penicillins, carbapenems, vancomycin and metronidazole in the medical ICU following the intervention (Rimawi et al., 2013).

A study in South Africa evaluating antimicrobial use in an ICU at an academic hospital found that meropenem, piperacillin-tazobactam and clarithromycin were the antibiotics most frequently prescribed in the ICU (Bester et al., 2017). This is similar to the current study, where meropenem, piperacillin-tazobactam and clarithromycin were among the most frequently used antibiotics in the ICU. This is also in concordance with the Surviving Sepsis Campaign, which advocates the use of a broad spectrum antibiotic as first-line therapy in patients with suspected sepsis (Dellinger et al., 2013).

A study on the prescribing patterns of a medical ICU at a teaching hospital in India found that cefotaxime, metronidazole, ampicillin and meropenem were the most commonly prescribed antimicrobials. In comparison, cefotaxime, metronidazole and ampicillin use was low in the study site ICU, and meropenem use was higher. Another study on AMS with the introduction of a specific antibiotic prescription chart resulted in a 19.6% reduction in antimicrobial consumption (Boyles et al., 2013). This study had the support of infectious diseases specialist which was not the case in the current study.
Figure 4.3.3: Antimicrobials used in the ICU (n=208)

For the medical ward, the use of amikacin, ceftriaxone, ciprofloxacin, meropenem and metronidazole decreased during the study period (refer to Figure 4.3.4). The use of amoxicillin-clavulanate, azithromycin, cefuroxime, clarithromycin and ertapenem increased during the study period.

Figure 4.3.4: Antimicrobials used in the medical ward (n=473)

The use of metronidazole decreased in both the ICU and medical ward during the study period, and this may be attributed to the AMS interventions made when the prescriber requested...
inappropriate double cover, such as amoxicillin-clavulenate plus metronidazole. This intervention was reinforced by training provided for the clinicians by the AMS committee on the inappropriate use of double cover antibiotics.

The use of macrolide antibiotics in both the medical ward as well as the ICU increased during the study period. Use of macrolides in the ICU was high as it was prescribed in critically ill patients with bacterial infection for its immunomodulatory properties, in accordance with IDSA guidelines for severe community-acquired pneumonia (CAP) (Wise et al., 2010).

If antibiotics prescribed in the ICU were compared to those prescribed in the medical ward, it can be seen that the ICU utilized more broad-spectrum antimicrobials than the medical ward. An increased usage of broad-spectrum antimicrobials is to be expected in the ICU setting, as this is in accordance with the Surviving Sepsis Campaign (Dellinger et al., 2013). The use of amoxicillin-clavulenate was higher in the medical ward than the ICU, as it is not regarded as appropriate empiric therapy in a critical care setting with multi-drug resistant organisms.

The study site does not adhere to any prescribing guidelines for antimicrobial therapy, therefore the choice of antimicrobial is left to the attending clinician. One of the initiatives of the AMS program during the study period, was to curb the inappropriate use of broad-spectrum antibiotics as first-line therapy. This intervention was made after a broad-spectrum was prescribed, using prospective audit with intervention and feedback. If the clinician rejected the intervention, the prescribed therapy was continued, as there was no infectious diseases physician available to intervene. De-escalation interventions were also proposed by the AMS pharmacist when culture results were available, usually within 72 hours.

4.4 Defined Daily Dose

The average DDD per 100 bed days for the control group was 25.08 and the average DDD per 100 bed days for the study group was 23.72 (refer to Table 4.4.1). For the ICU, the average DDD per 100 bed days for the control group was 16.38 and the average DDD per 100 bed days for the study group was 12.67 (refer to Table 4.4.2). For the medical ward, the average DDD per 100 bed days for the control group was 33.77 and the average DDD per 100 bed days for the study group was 34.77 (refer to Table 4.4.3).

There was an overall decrease in DDD per 100 bed days from the control group to the study group of 1.36. The decrease in DDD per 100 bed days between the control group and the study group was not statistically significant (p value=0.8169). For the ICU, there was a
decrease in DDD per 100 bed days between the control group and the study group of 3.71. This may be attributed to the bulk of the AMS pharmacist time on AMS being spent in this unit, as well as the ICU being a closed unit under the direct management of an ICU intensivist.

For the medical ward, there was an increase in DDD per 100 bed days between the control group and the study group of 1. The DDDs for individual agents for the two wards included in the study were not available. The hospital has selective individual agents DDD data, however this is for the entire hospital and not just the two wards in this study. Therefore, data for DDDs for individual antibiotics could not be presented. A recent AMS implementation study across 47 private South African hospitals resulted in a significant decrease (18.34) in DDD per 100 bed days (Brink et al., 2016). This study was conducted over a five-year period. Our study does not correlate with the above findings, however, our study period was very brief and only evaluated the impact of an AMS programme in two wards.

Table 4.4.1: DDD per 100 bed days

<table>
<thead>
<tr>
<th>Population</th>
<th>MEAN DDD per 100 bed days</th>
<th>STD DEV</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Group</td>
<td>25.08</td>
<td>15.67</td>
<td>6.50</td>
<td>51.70</td>
</tr>
<tr>
<td>(n=254)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Group</td>
<td>23.72</td>
<td>13.05</td>
<td>7.90</td>
<td>47.00</td>
</tr>
<tr>
<td>(n=427)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4.4.2: ICU DDD per 100 bed days

<table>
<thead>
<tr>
<th>Population</th>
<th>Jan</th>
<th>Feb</th>
<th>Mar</th>
<th>April</th>
<th>May</th>
<th>June</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Group</td>
<td>27</td>
<td>12,3</td>
<td>10,5</td>
<td>29,6</td>
<td>6,6</td>
<td>12,3</td>
<td>16,38</td>
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<tr>
<td>(n=52)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Group</td>
<td>12</td>
<td>7,9</td>
<td>14,2</td>
<td>13,6</td>
<td>14,8</td>
<td>13,5</td>
<td>12,67</td>
</tr>
<tr>
<td>(n=156)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4.4.3: Medical Ward DDD per 100 bed days

<table>
<thead>
<tr>
<th>Population</th>
<th>Jan</th>
<th>Feb</th>
<th>Mar</th>
<th>April</th>
<th>May</th>
<th>June</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Group</td>
<td>51,7</td>
<td>26,6</td>
<td>48,6</td>
<td>36,3</td>
<td>6,5</td>
<td>32,9</td>
<td>33,77</td>
</tr>
<tr>
<td>(n=202)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Group</td>
<td>47</td>
<td>20,9</td>
<td>39,8</td>
<td>34</td>
<td>31,9</td>
<td>35</td>
<td>34,77</td>
</tr>
<tr>
<td>(n=271)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4.5 *Clostridium difficile* infection rate

The *Clostridium difficile* infections (CDI) rate for the control group was 1.94 and the CDI rate for the study group was zero, as no hospital-acquired CDI occurred during the study period. For the control group, two hospital acquired *Clostridium difficile* infections occurred during the study period and for the study group, no hospital-acquired CDI occurred during the study period. The reduction in CDI rate between the control group and the study group was not statistically significant (p=0.1417). The CDI rate reduction for this study cannot be attributed to the AMS programme because, although there were no *Clostridium difficile* infections during the study period, the hospital has an active infection control programme and this could have resulted in a decrease in the CDI rate.

A study in Ireland evaluating the restriction of high-risk antibiotics on the incidence of CDI found a significant reduction in the incidence of CDI. It should be noted that this study was conducted over a period of 6.5 years. The restriction of the high-risk antibiotics contributed to both a reduction in their use and a reduction in the incidence of CDI in the study site hospital (Aldeyab et al., 2012).

A study in the UK evaluated the impact of guidelines and an enhanced AMS programme on the use of broad-spectrum antibiotics and the incidence of CDI and found that these interventions were associated with a significant decrease in CDI (Talpaert et al., 2011). This study developed guidelines on restricting broad-spectrum antimicrobials use in consultation with senior clinicians and microbiology surveillance data. Broad-spectrum antimicrobials were restricted and removed from wards to prevent access. The restriction of certain antimicrobials was not possible at our study site at the time of the study.

4.6 Days of therapy

The duration of therapy was calculated using actual number of days of antimicrobial therapy for each patient in both groups. The average duration of therapy for the control group was 4.84 days and 4.69 days for the study group (refer to Table 4.6.1). For ICU patients, the average duration of therapy for the control group was 4.75 days and for the study group it was 4.87 days (refer to Table 4.6.2). For medical ward patients, the average duration of therapy for the control group was 4.87 days and for the study group was 4.59 days (refer to Table 4.6.3). The difference in DOT between the control group and the study group was not statistically significant (p-value = 0.5485).
The calculation of the days of therapy was done using actual number of days of antibiotic therapy per patient per ward, for both the study group and the control group. Calculating days of antimicrobial therapy is labour-intensive and not a feasible option for resource-limited settings, or small hospitals, as this requires the AMS pharmacist to count the actual doses of each antimicrobial agent administered to each patient. The study site does not have access to rapid testing diagnostic kits for diagnosis of bacterial infections, therefore empiric antimicrobial therapy continues until the various culture results are available from the laboratory, which can take between 3-5 days. This had an impact on the number of days of antimicrobial therapy as the ward pharmacist could not make any intervention to change the therapy or reduce the number of days of treatment until the results were available.

A study evaluating the impact of an AMS programme prospective audit and review at a community hospital in the surgical, respiratory and medical wards in Canada found that antibiotic use decreased by 91 DOT/1000 patient days in the medical ward. This decrease was sustained up to 50 months after the initiation of the intervention, and also resulted in decreased antibiotic costs (Campbell et al., 2017). This study was for a much longer duration than the current study, and had a long-established AMS programme.

A Brazilian study evaluating the impact of early discontinuation of intravenous antibiotics by the AMS team found that the decrease in duration of intravenous antimicrobial therapy was not statistically significant (Bonella et al., 2016). This study is similar to our study, in terms of the control group and the intervention group, and was also conducted in a developing country and the clinical pharmacist did not have the support of an infectious diseases practitioner.

<table>
<thead>
<tr>
<th>Population</th>
<th>Number</th>
<th>Mean days of therapy</th>
<th>STD DEV</th>
<th>STD ERR</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Group</td>
<td>254</td>
<td>4.84</td>
<td>3.65</td>
<td>0.23</td>
<td>2.0</td>
<td>36.0</td>
</tr>
<tr>
<td>Study Group</td>
<td>427</td>
<td>4.69</td>
<td>2.18</td>
<td>0.11</td>
<td>2.0</td>
<td>15.0</td>
</tr>
</tbody>
</table>
Table 4.6.2: Days of therapy for ICU

<table>
<thead>
<tr>
<th>Population</th>
<th>Number</th>
<th>Days of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group (2013)</td>
<td>52</td>
<td>4.75</td>
</tr>
<tr>
<td>Study group (2015)</td>
<td>156</td>
<td>4.87</td>
</tr>
</tbody>
</table>

Table 4.6.3: Days of therapy for medical ward

<table>
<thead>
<tr>
<th>Population</th>
<th>Number</th>
<th>Day of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group (2013)</td>
<td>202</td>
<td>4.87</td>
</tr>
<tr>
<td>Study group (2015)</td>
<td>271</td>
<td>4.59</td>
</tr>
</tbody>
</table>

4.7 Antimicrobial cost

Cost data, using 2013 acquisition costs for both the control and study group, was utilized to determine the cost of therapy per patient per antimicrobial. The total costs were analysed to determine if the implementation of an AMS programme resulted in cost savings. The increase in the number of patients were compared for the ICU and medical ward from 2013 to 2015, as this would impact the cost data. Finally, the cost per patient for the ICU and medical ward were compared between 2013 and 2015. There was an increase in cost per patient between the control group and the study group. The total increase in cost per patient between the control group and the study group was R743.61.

For the ICU, although there was a 28.3% increase in cost per patient, a 269.9% increase in the total cost of antimicrobials and a 414.8% increase in the number of antimicrobials used, the number of patients increased by 200%. The latter three components increased far more in comparison to the 28.3% increase in cost per patient (refer to Table 4.7.1).

Table 4.7.1: Cost analysis between control group and study group - ICU

<table>
<thead>
<tr>
<th>Category</th>
<th>Control Group</th>
<th>Study Group</th>
<th>Percentage (%) change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>52</td>
<td>156</td>
<td>200.0%</td>
</tr>
<tr>
<td>Number of antibiotics</td>
<td>593</td>
<td>3053</td>
<td>414.8%</td>
</tr>
<tr>
<td>Total cost of antibiotics</td>
<td>R 115 622.65</td>
<td>R 427 745.98</td>
<td>269.9%</td>
</tr>
<tr>
<td>Cost per patient</td>
<td>R 2 223.51</td>
<td>R 2 851.80</td>
<td>28.3%</td>
</tr>
</tbody>
</table>
For the medical ward, although there was an 10.9% increase in cost per patient and an 48.8% increase in the total cost of antimicrobials, the number of patients increased by 34.2%. The increase in cost per patient is less than the 34.2% increase in the number of patients (refer to table 4.7.2).

Table 4.7.2: Cost analysis between control group and study group – Medical ward

<table>
<thead>
<tr>
<th>Category</th>
<th>Control Group</th>
<th>Study Group</th>
<th>Percentage (%) change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>202</td>
<td>271</td>
<td>34.2%</td>
</tr>
<tr>
<td>Number of antibiotics</td>
<td>2778</td>
<td>3596</td>
<td>29.4%</td>
</tr>
<tr>
<td>Total cost of antibiotics</td>
<td>R213 833.16</td>
<td>R 318 126.90</td>
<td>48.8%</td>
</tr>
<tr>
<td>Cost per patient</td>
<td>R 1 058.58</td>
<td>R 1 173.90</td>
<td>10.9%</td>
</tr>
</tbody>
</table>

From the above, it can be seen that the implementation of an AMS programme at the study site did not result in cost savings, and costs actually increased in the study period. However, this study did not evaluate indirect cost savings, such as the amount of money saved due to decreased use of certain antimicrobial agents, or the cost savings due to decreased length of hospital stay, or cost savings due to decreased days of antibiotic therapy, or decreased acquisition of multi-drug resistant infections, which all contribute to a decrease in cost.

Cost comparisons are not the most reliable measure for AMS outcomes as cost varies from hospital-to-hospital and region-to-region. The cost data utilized for the study was the cost of antimicrobial acquisition by the hospital pharmacy in 2013. The cost data for 2013 was used for both the control group as well as the study group.

There are no studies in SA that compared cost savings due to an AMS programme in the same manner as this study. However, in comparison to similar studies, a pre–post analysis of an antimicrobial stewardship programme resulted in significant cost savings as well as a significant decrease in DDD (Nowak et al., 2012; Bantar et al., 2003). The first study investigated the impact of AMS over a 3-year period and the second study had a 3-phase implementation stage.

4.8 Summary

In this chapter, the results of the study were presented and discussed according to the objectives of the study and compared with published literature. Patient demographics, such as age and gender were comparable for both the groups. Antimicrobials prescribed were
compared for the control period and the study period, as well as the variations between prescribing in the ICU and the medical ward. The diagnosis for both the groups were comparable, and it was found that pneumonia was the most common diagnosis for both groups. There was a non-significant decrease in both DDD and DOT. The decrease in CDI rate could not be attributed to the AMS programme, as there were no CDI cases during the study period. The cost of therapy increased in the study period, therefore the AMS programme did not result in cost savings.
CHAPTER 5

SUMMARY, LIMITATIONS, RECOMMENDATIONS AND CONCLUSION

5.1 Introduction

In this chapter, the summary of the results discussed will be presented. Based on the results of the study, recommendations for practice will be offered, as well as the limitations encountered during the study. The chapter will end with the conclusion.

5.2 Summary of results

A total of 681 patient files were reviewed for this study. The control group (2013) comprised of 254 patients. The study group (2015) comprised of 427 patients. Two wards were utilized for the study, the ICU and medical ward, as these are the wards with the highest antimicrobial consumption at the study site, and therefore the bulk of the AMS pharmacists' time was spent in these wards.

The study population comprised of 43.9% males and 56.1% females (n=681). The mean age for the study group was 62.6 years and the mean age for the control group was 64.9 years. There were no statistically significant differences in the gender (p=0.5775) and age (p=0.1257) of the control group in comparison to the study group.

The most common diagnosis for the control group as well as the study group was pneumonia. Both the control group and the study group shared similar infectious diagnosis. The diagnosis for both groups were comparable.

For antibiotic use, although there was a decrease in the prescription of Gram-positive as well as Gram-negative antimicrobials, there was an increase in the prescription of broad spectrum cover. This is in keeping with current guidelines on initial broad spectrum antimicrobial therapy, however, it is an area that needs to be actively monitored and, if necessary, addressed by the AMS programme, as broad spectrum antimicrobials may contribute to the increase in antimicrobial resistance.

Amoxicillin-clavulanate was the most commonly prescribed antimicrobial for both the control group and the study group. The most commonly prescribed antimicrobials for the control group were amoxicillin-clavulanate, ceftriaxone, metronidazole, ciprofloxacin, meropenem and
piperacillin-tazobactam. In comparison, the most commonly prescribed antimicrobials for the study group were amoxicillin-clavulanate, clarithromycin, ertapenem, piperacillin-tazobactam and cefuroxime.

The differences in antimicrobials prescribed between the ICU and the medical ward is a reflection of the infections seen in these wards. The ICU reflected a higher utilization of broad spectrum cover in comparison to the medical ward, and this was in accordance with best practice guidelines.

There was a non-significant decrease in DDD per 100 bed days from the control group to the study group of 1.36 (p=0.8169). There was a reduction of 3.71 DDD per 100 bed days in the ICU. There was an increase of 1 DDD per 100 bed days in the medical ward. The study period was quite brief and there was only one AMS pharmacist carrying out AMS activities, which could explain why the decrease was not statistically significant. A longer study period may provide a clearer picture of the impact of an AMS programme on antimicrobial DDD.

The reduction in CDI rate between the control group and the study group was not statistically significant (p=0.1417). This reduction cannot be attributed to the AMS programme, as there were no CDI cases during the study period, and this may be due to the short study duration or may be attributed to the effects of an active infection prevention and control programme at the study site.

The DOT decreased by 0.15 and this was not statistically significant (p-value= 0.5485). For the ICU, the DOT increased by 0.12. For the medical ward, the DOT decreased by 0.28.

The cost of therapy increased during the study period. The total increase in cost per patient between the control group and the study group was R743.61. The cost per patient in the ICU increased by 28.3% and the cost per patient in the medical ward increased by 10.9%.

From the results, it is apparent that this AMS programme did not have a significant impact on the study objectives. The study results were also not concordant with current literature on the impact of similar AMS programmes on antibiotic utilization. The patient demographics, diagnosis and antimicrobials used were similar to the results of other AMS studies in the literature, as discussed in Chapter 4. However, the main objectives of the study indicated that the AMS programme did not result in a significant decrease in antimicrobial use, DDD, DOT, CDI rate and cost of therapy.
A recent AMS implementation study across 47 private South African hospitals resulted in a significant decrease (18.34) in DDD per 100 bed days (Brink et al., 2016). The current study only resulted in a decrease of 1.36 DDD’s (p=0.8169). A study in the UK evaluated the impact of guidelines and an enhanced AMS programme on the use of broad-spectrum antibiotics and the incidence of CDI and found that these interventions were associated with a significant decrease in CDI (Talpaert et al., 2011), however the current study did not have a significant reduction in CDI rate (p=0.1417). Another study evaluating the impact of an AMS programme prospective audit and review in Canada found that antibiotic use decreased by 91 DOT/1000 patient days (Campbell et al., 2017) whereas the current study only found a decrease in DOT of 0.15 and this was not statistically significant (p-value= 0.5485). The cost of therapy went up for the current study, however a similar pre-post AMS implementation study resulted in significant cost savings as well as a significant decrease in DDD (Nowak et al., 2012; Bantar et al., 2003). It can be seen from this study that implementing an AMS programme does not guarantee a decrease in DDD, DOT, CDI rate and antimicrobial cost.

5.3 Limitations and recommendations of the study

The following limitations and recommendations were made based on the results of the study:

- The period of study was very brief (6 months) and it is recommended that a longer study period may result in more balanced outcomes.
- The implementation of an AMS programme was very recent, and may need to be well established before significant impact may be observed.
- The study only looked at the impact of AMS implementation in two wards. Further studies investigating the impact of AMS on the total hospital population may be a better indicator.
- The study focused on the implementation of AMS as a whole and therefore improvement and/or change cannot be attributed to the implementation of a specific measure.
- Length of stay, morbidity and mortality were not investigated in the study, and it is recommended that the impact of an AMS programme on these outcomes be investigated in future AMS studies.
- Although an antimicrobial stewardship programme was implemented at the study site, this did not require every clinician at the site to conform to the guidelines and recommendations implemented by this committee, which affected the outcome and
progress of the AMS programme. South Africa has a unique private sector healthcare environment. Clinicians are not employed by the hospital group and rather work independently at the various private hospitals. Not being an employee of the hospital allows clinicians the advantage of not having to abide by the guidelines implemented by these hospitals, including those of the AMS programme. AMS programme involvement is voluntary and often overlooked by clinicians.

5.4 Conclusion

The introduction of an antimicrobial stewardship committee has many benefits in the hospital setting as should be an essential component of any healthcare system. Further, high-quality studies of the impact of AMS programmes in the South African setting are needed as there is a paucity of published studies on outcomes in AMS.

The implementation of an AMS programme in a private hospital setting did not result in a significant decrease in the DDD, DOT and CDI rate, and resulted in an increase in the cost of antimicrobial therapy per patient.

However, AMS is currently in its infancy in this country and further studies in this setting is required and for a longer duration, as the success of an AMS programme requires a change in the mindset and culture of the prescribing clinicians and changing the culture of an institution requires time.
CHAPTER 6

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   http://dx.doi.org/10.1016/S1473-3099(16)30012-3


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56. Stats SA. 2015. Statistics South Africa (Stats SA)


APPENDICES

Appendix 1: Data Collection Sheet for study patients and control group patients

<table>
<thead>
<tr>
<th>WARD</th>
<th>PATIENT STUDY NUMBER</th>
<th>AGE</th>
<th>GENDER</th>
<th>ICD-10 CODE</th>
<th>ANTIBIOTIC ADMINISTERED</th>
<th>DAYS OF THERAPY</th>
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Appendix 2: Data Collection sheet for defined daily dose (DDD) data

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<th>ICU DDD</th>
<th>MEDICAL WARD DDD</th>
<th>HOSPITAL DDD</th>
<th>ANTIBIOTIC EXPENDITURE</th>
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Appendix 3: Letter of Intent for permission to conduct the study

Netcare Rosebank Hospital

Dear Linda Bessert

23 February 2016

Request for permission to conduct a study at Netcare Rosebank Hospital

I am a post-graduate student at the Department of Pharmacy of Sefako Makgatho University of Health Sciences. As part of the requirements of my MPharm post-graduate qualification, I have to conduct a research project. The title of my study is “The impact of antimicrobial stewardship on antibiotic use - a retrospective review in a private hospital, Johannesburg, Gauteng”.

I kindly request your permission to conduct the study at Netcare Rosebank Hospital. Please see attached a copy of my protocol which will be submitted to Netcare’s research committee as well as the Sefako Makgatho University of Health Sciences Research and Ethics committee for approval.

I trust that you will find the above in order. Please feel free to contact me or my supervisor, Prof Gous and Dr. Schellack should you require additional information. (Dr. N. Schellack: 0125213286)

Yours faithfully,

Mrs Aisha Kala

Netcare Rosebank Hospital
Hospital General Manager

23 FEB 2016

Apprentice
Sefako Makgatho Health Sciences University
Research & Postgraduate Studies Directorate
Sefako Makgatho University Research Ethics Committee
(SMUREC)

Molotlegi Street, Ga-Rankuwa 0208
Tel: (012) 521 5617/3698 | fax: (012) 521 3749
Email: lorato.phiri@smu.ac.za
P.O. Box 163 Medunsa 0204

APPORVAL NOTICE - NEW APPLICATION

07 April 2016
Ms A Mahomeddi
Department of Pharmacy
P.O Box 218
Medunsa, 0204

MEETING:
03/2016

SMUREC Ethics Reference Number: SMUREC/H7/1/2016: PG

The New Application received on 17 March 2015, was reviewed by members of Sefako Makgatho University Research Ethics Committee 07 April 2016 and was approved on 07 April 2016.

Title: The Impact of antimicrobial stewardship on antibiotic use - a retrospective review in a private hospital, Johannesburg, Gauteng.

Researcher: Ms A Mahomeddi
Supervisor: Prof AGS Gous
Co-supervisor: Prof N Schellack
Health Care Manager: Ms L Dossert (Netcare Roebark Hospital)
Department: Pharmacy
School: Health Care Sciences
Degree: Masters of Pharmacy

Please note the following information about your approved research protocol:

Protocol Approval Period: 07 April 2016 – 07 April 2017

Please remember to use your protocol number (SMUREC/H7/1/2016: PG) on any documents or correspondence with the REC concerning your research protocol.

Please note that the REC has the prerogative and authority to ask further questions, seek additional information, require further modification, or monitor the conduct of your research and the consent process.

After Ethical Review: Please note a template of the progress report is obtainable in the Research Office and should be submitted to the Committee before the year has expired. The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit. Translation of the consent document in the language applicable to the study participants should be submitted.


Sincerely,

[Signature]
DR C Baker
DEPUTY CHAIRPERSON SMUREC

Sefako Makgatho
Health Sciences University
SMU Research Ethics Committee
Chairperson

Date: 07 April 2016
Appendix 5: Study site approval

RESEARCH OPERATIONS COMMITTEE FINAL APPROVAL OF RESEARCH

Approval number: UNIV-2016-0028

Ms Aisha Kala

E mail: Aisha.Kala@netcare.co.za; Aisha.Kala@icloud.com

Dear Ms Kala

RE: THE IMPACT OF ANTIMICROBIAL STEWARDSHIP ON ANTIBIOTIC USE - A RETROSPECTIVE REVIEW IN A PRIVATE HOSPITAL, JOHANNESBURG, GAUTENG

The above-mentioned research was reviewed by the Research Operations Committee's delegated members and it is with pleasure that we inform you that your application to conduct this research at Netcare Rosebank Hospital, has been approved, subject to the following:

i) Research may now commence with this FINAL APPROVAL from the Netcare Research Operations Committee.

ii) All information regarding Netcare will be treated as legally privileged and confidential.

iii) Netcare's name will not be mentioned without written consent from the Netcare Research Operations Committee.

iv) All legal requirements regarding patient / participant's rights and confidentiality will be complied with.

v) The research will be conducted in compliance with the GUIDELINES FOR GOOD PRACTICE IN THE CONDUCT OF CLINICAL TRIALS IN HUMAN PARTICIPANTS IN SOUTH AFRICA (2006)

vi) Netcare must be furnished with a STATUS REPORT on the progress of the study at least annually on 30th September irrespective of the date of approval from the Netcare Research Operations Committee as well as a FINAL REPORT with reference to intention to publish and probable journals for publication, on completion of the study.
vii) A copy of the research report will be provided to the Netcare Research Operations Committee once it is finally approved by the relevant primary party or tertiary institution, or once complete or if discontinued for any reason whatsoever prior to the expected completion date.

viii) Netcare has the right to implement any recommendations from the research.

ix) Netcare reserves the right to withdraw the approval for research at any time during the process, should the research prove to be detrimental to the subjects/Netcare or should the researcher not comply with the conditions of approval.

x) APPROVAL IS VALID FOR A PERIOD OF 36 MONTHS FROM DATE OF THIS LETTER OR COMPLETION OR DISCONTINUATION OF THE TRIAL, WHICHEVER IS THE FIRST.

We wish you success in your research.

Yours faithfully,

[Signature]

Prof Dion du Plessis
Full member: Netcare Research Operations Committee & Medical Practitioner evaluating research applications as per Management and Governance Policy

Shannon Neil
Chairperson: Netcare Research Operations Committee

Netcare Hospitals (Pty) Ltd

Date: 20/6/2016