EFFECTS OF ANTIMICROBIAL STEWARDSHIP POLICY IN IMPROVING ANTIBIOTIC UTILISATION AND REDUCING DRUG COSTS IN A PUBLIC HOSPITAL IN GAUTENG PROVINCE, SOUTH AFRICA

By

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DECLARATION

I, Muhammad Augie Bashar declare that this dissertation is my original work. Contributions made by other people to this body of work have been duly acknowledged. It is being submitted for the degree of Masters of Medicine (Pharmacology) at the University of the Witwatersrand, Johannesburg, South Africa. It has not been submitted before for any degree or examination at this or any other University.

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Signature

Muhammad Augie Bashar

Signed on ……15th November, 2017.

DEDICATION

I dedicate this work to my loving parents, wife, kids and siblings for your prayers, support, patience and commitment.

CONFERENCE PROCEEDINGS

1. Bashar M.A, Miot J, Shoul E, and van Zyl R.L. Review of antibiotic utilisation and costs in a public hospital in Gauteng Province, South Africa. Poster presentation at the All Africa Congress on Pharmacology and Pharmacy, 5 to 8 October 2016, Misty Hills and Conference Centre, Muldersdrift, Gauteng, South Africa.
2. Bashar Augie, Jacqui Miot, Evan Shoul, and Robyn van Zyl. Improving antibiotic utilisation in surgery wards. Oral presentation at the 2017 Annual General Scientific Conference of the Nigerian Infectious Diseases Society, 9 to 10 November 2017, Ayalla Hotels Ltd off Ahmadu Bello Way Garki, Area 11, Abuja, Nigeria.
3. Bashar M. Augie, Jacqui Miot, Evan Shoul, and Robyn L. van Zyl. Impact of an antimicrobial stewardship ward round in a surgical ward setting. Poster presentation at the Antimicrobial resistance symposium, organised by the Nigerian Centre for Disease Control and Prevention 14 to 16 November 2017, Transcorp Hilton Abuja, Nigeria.

ABSTRACT

Antimicrobial stewardship (AMS) programmes along with infection and prevention control measures have been shown to reduce the burden of antimicrobial resistance (AMR) in hospitals. There is a global campaign by infectious diseases physicians and other stakeholders for hospitals to implement AMS programmes. In Africa, there have been a limited number of AMS studies conducted although South African private hospitals have published some outcomes on initiation of these programmes in the continent, with the aim of improving patients' clinical outcomes and reducing the development of resistance to prescribed antibiotics. A formal AMS programme is yet to be implemented in the surgery departments of the Charlotte Maxeke Johannesburg Academic Hospital.

This study was conducted in two surgical wards of the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). It was a quantitative study combining a prevalence cross-sectional observational stage, and an intervention study. It involved a retrospective review of patient records in the baseline stage followed by an intervention which took the form of a weekly antibiotic round led by an infectious diseases specialist. The appropriateness of antibiotic prescriptions was assessed using the criteria developed by Gyssens and colleagues, while the appropriateness of surgical prophylaxis was determined based on the recommendations of the South African Antibiotic Stewardship Programme (SAASP) and current Standard Treatment Guidelines and Essential Medicines Lists for South Africa. The prices of the antibiotics used were obtained from the central pharmacy of the CMJAH and Masters Price Catalogue list of the National Department of Health, while the prices of laboratory tests were obtained from the Tariff database. The volume of antibiotics consumed was determined by Defined Daily Doses (DDDs)/1000 patient days.

In both stages of the study amoxicillin/clavulanic acid was the most frequently used agent. The intravenous route was the most commonly used route of drug administration in both stages of the study. There was a reduction in the proportion of patients who were treated with antibiotics for more than seven days in the intervention stage, from 6.19% in the baseline stage to 2.07% in the intervention stage. A significant reduction in the duration of antibiotic therapy for two days and more was observed from

4.74 ± 4.58 days in the baseline stage compared to 3.96 ± 2.04 days in the intervention stage (p = 0.01). A shift from empiric to culture directed therapy was also observed in the intervention stage compared to the baseline stage. There was a significant reduction in the volume of antibiotic consumption from a total of 739.30 DDDs/1000 patient days in the baseline stage to 564.93 DDDs/1000 patient days in the intervention stage (p = 0.038). Overall, there was a significant reduction of inappropriate antibiotic utilisation from 35% in the baseline stage to 26% in the intervention stage (p = 0.006). A high percentage of inappropriate surgical prophylaxis was found which was mostly due to the incorrect choice of agent with 64.75% and 61.54% in the baseline and intervention stages, respectively. The average antibiotic cost per patient was reduced from R 268.23 ± 389.32 to R 228.03 ± 326.88 in the Vascular Surgery Ward compared to the General Surgery Ward where there was an increase in average cost per patient from R 219.80 ± 400.75 in the baseline stage to R 284.06 ± 461.28 in the intervention stage. Gram-negative bacteria were the most prevalent pathogens in both stages of the study at 53% in the baseline and 54% during the intervention stage.

The findings of this study show an improvement in the appropriateness of antibiotic utilisation, reduction in antibiotic consumption and cost reduction in one of the study wards, following implementation of an AMS programme. Also, there was an improvement in culture directed therapy, requests for an appropriate biological specimen for culture, with a consequent increase in the cost of laboratory investigations per patient during the intervention stage, which was due to increases in culture request. Rational antimicrobial prescribing habits, strong AMS interventions along with infection and prevention control measures, sound government policies and surveillance of resistant organisms in Africa will go a long way in preserving our antibiotics and preventing the spread of multidrug-resistant pathogens.

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LIST OF ABBREVIATIONS

ADT : Antimicrobial Drug Therapy
AMR : Antimicrobial Resistance
AMS : Antimicrobial Stewardship
ATC : Anatomical Therapeutic Chemical
BCA : Best Care Always
BRICS : Brazil, Russia, India, China, and South Africa
CDC : Centre for Disease Control and Prevention
CEO : Chief Executive Officer
CRP : C - reactive protein
CMJAH : Charlotte Maxeke Johannesburg Academic Hospital
CRE : Carbapenem-Resistant *Enterobacteriaceae*
DDDs : Defined Daily Doses
DOT : Days of Therapy
DoTh : Duration of Therapy
DNA : Deoxyribonucleic acid
DUR : Drug Utilisation Review
EMA : European Medicines Agency
FBC : Full Blood Count
FDA : Food and Drug Administration
FTEs : Full-time equivalents
GARP : Group for Antibiotic Resistance Partnership
GBLCs : Gallbladder Biliary-Tract and Liver Cases
HIV : Human Immunodeficiency Virus
hVISA : Heterogeneous Vancomycin Intermediate *Staphylococcus aureus*
ICU : Intensive Care Unit
IDSA : Infectious Diseases Society of America
IV : Intravenous
LGCs : Lower Gastrointestinal Cases
MCS : Microscopy Culture and Sensitivity
mrc-1 : Mannose receptor, C type 1
MRSA : Methicillin-Resistant *Staphylococcus aureus*
MSSA : Methicillin-Sensitive *Staphylococcus aureus*

NDM-1 : New Delhi Metallo-Beta-lactamase-1

NDoH : National Department of Health

NHLS : National Health Laboratory Service

OR : Odds ratio

PCT : Procalcitonin

PBPs : Penicillin-Binding Proteins

RCTs : Randomised Control Trials

SAASP : South African Antibiotic Stewardship Programme

SSIs : Surgical Site Infections

SUs : Standard Units

UGCs : Upper Gastrointestinal Cases

USA : United State of America

UTI : Urinary Tract Infection

VRE : Vancomycin-Resistant *Enterococci*

VRSA : Vancomycin-Resistant *Staphylococcus aureus*

WCC : White Cell Count

PREFACE

"Today, antibiotics are rarely prescribed based on a definitive diagnosis. Diagnostic tests can show whether or not an antibiotic is actually needed, and which one. Having rapid, low-cost, and readily available diagnostics is an essential part of the solution to this urgent problem."

Dr Margaret Chan, Director-General of the World Health Organization (O'Neill, 2016).

"A crucial part of tackling this challenge is to create the circumstances for behavioural change. From reducing smoking rates, to convincing people to wear seatbelts, effective public campaigns have repeatedly changed social attitudes and improved human health. In this case, a public health campaign has the potential to build understanding and change behaviour, helping to avoid a future catastrophe that could see 10 million people dying every year."

Donald A. Baer, Worldwide Chair and CEO, Burson-Marsteller (O'Neill, 2016).

"Tackling antimicrobial resistance requires a wide range of approaches and developing alternatives to antibiotics, in humans and animals, is critical to the fight. Vaccines have a vital role to play in combatting drug resistance, by preventing infections in the first place."

Dame Sally Davies, Chief Medical Officer for England (O'Neill, 2016).

"The basics of public health – clean water, good sanitation and hygiene, infection prevention and control and surveillance – are as critical for reducing the impact of antimicrobial resistance as they are for infectious disease control. While we also need new technologies and medicines, and better use of existing medicines, we cannot let attention to fundamental public health practices suffer, or else antimicrobial resistance will continue to thrive."

Dr Keiji Fukuda, the Director General's Special Representative for Antimicrobial Resistance at the World Health Organization (WHO) (O'Neill, 2016).

"Without good surveillance, we cannot effectively counter the threat that antimicrobial resistance poses to health systems and people all over the world. It is also vital that countries work together to make sure old and new technologies are rolled out in a way

that supports better global One Health AMR surveillance including animals and the environment."

Yasuhisa Shiozaki, Minister of Health, Labour and Welfare for Japan (O'Neill, 2016).

"Infectious Diseases and Microbiology are among the least subscribed specialities in medicine and research, this leading to a shortage of key personnel on the frontlines of the challenge of drug-resistant infections. This needs to change immediately if we are to turn the tide against rising resistance."

Dr Jeremy Farrar, Director, Wellcome Trust (O'Neill, 2016).

"We have to dramatically shift incentives for pharmaceutical companies and others to create a long-term solution to this problem, with new rewards, funded globally, that support the development of new antibiotics and ensure access to antibiotics in the developing world."

George Osborne, Chancellor of the Exchequer, United Kingdom (O'Neill, 2016).

CHAPTER ONE: OVERVIEW OF THE STUDY

1.1 INTRODUCTION

Before the discovery of antibiotics, patients were dying from simple bacterial infections (Donaldson, 2009), however, since their discovery more than seven decades ago, antibiotics have saved millions of lives globally (CDC, 2013). Almost half of hospitalised patients have been reported to receive antibiotics during their inpatient stay in the United States (Owens, 2009). Even higher rates have been reported in China, ranging from 85% to 100% (Sweidan *et al.,* 2005). In its 2013 annual report on global risks, the World Economic Forum reported that the biggest public health risk facing humankind was hard-to-treat bacterial infections (World Economic Forum, 2013). Ways to address this challenging issue include paying attention to infection and prevention control measures, antimicrobial stewardship programmes and encouraging new economic models to promote research and development of new antibacterial agents (Howell, 2013).

1.1.1 Antimicrobial resistance

Antimicrobial resistance (AMR) is an ancient survival strategy adopted by microorganisms such as bacteria to withstand treatment with antimicrobial agents (D'costa *et al.,* 2011; NDoH, 2014b). Microorganisms are an important component of this planet; playing an important function in striking a balance of the ecosystem. Microorganisms have lived for more than 3.8 billion years, making up nearly 50% of all living organisms and have over the years manifested various genetic and metabolic strategies to survive harsh environmental conditions (Byarugaba, 2010; Ramsamy *et al.*, 2016). Boseley (2010) reported that AMR follows the concept of the Darwinian theory of natural selection - identification of mutant bacterial genes from a 30,000-year-old pergélisol residue in Yukon indicates that AMR precedes modern day antibiotics (D'costa *et al.,* 2011).

Antibiotic resistance is an unavoidable occurrence but can be delayed by adopting programmes that encourage appropriate antibiotic utilisation (Gould,

2009). To curtail the menace of AMR, the Infectious Diseases Society of America (IDSA) in 2010 proposed that the global community needs to adopt Antimicrobial Stewardship (AMS) programmes to optimise the use of antibiotics. IDSA also encouraged the pharmaceutical industries to develop ten new antibacterial agents by 2020 (IDSA, 2010). Prof J O'Neill and colleagues in their report proposed a quick release of a US$ 2 billion innovation fund to revitalise research and development of new antibiotics (O'Neill, 2016).

One of the causes of AMR is inappropriate surgical prophylaxis, however, when appropriately implemented surgical prophylaxis has been shown to reduce the chances of developing surgical site infections (SSIs) (Bowater *et al.*, 2009; Enzler *et al.*, 2011). Of note, surgical prophylaxis is not a substitute for standard infection control measures (Bratzler *et al.*, 2013). A multicentre AMS initiative, led by non-specialised pharmacists significantly improved adherence to a peri-operative antibiotic prophylaxis bundles which in turn led to a significant reduction in SSI rates across a large network of diverse urban and rural hospitals in South Africa (Brink *et al.*, 2017). The updated American surgical prophylaxis guideline of 2013, recommends the use of an agent with bactericidal and in vivo activities on common pathogens causing SSIs after an operation (Bratzler *et al.*, 2013). The United States guideline also recommends the use of a surgical prophylactic agent for less than 24 hours, thereby reducing cost, adverse events and AMR (Bratzler *et al.*, 2013).

1.1.2 **Antimicrobial stewardship**

Very little data are available on the implementation of AMS activities on the African continent (Brink *et al.,* 2016a). In a joint statement, the Society for Healthcare Epidemiology of America, the IDSA and the Paediatric Infectious Diseases Society defined AMS as *"Coordinated interventions designed to improve and measure the appropriate use of an antimicrobial agents by promoting the selection of the optimal antimicrobial drug regimen including dosing, duration of therapy and route of administration"* (Fishman, 2012). An AMS programme involves many strategies with different approaches and when properly conducted will impact positively on patient clinical outcomes (Davey *et al.*, 2017). It is an essential tool for preserving the value of current and subsequent generations of antibiotics (Tillotson, 2015). The main aim of AMS

programmes is to ensure patients receive appropriate antibiotic therapy, improved clinical response and tolerable adverse reactions, along with reducing costs associated with inappropriate antibiotic use (Fishman, 2012). A pharmacist-driven prospective audit and feedback model across a diverse group of 47 urban and rural South African hospitals, has recorded a sustainable reduction in overall antibiotic consumption (Brink *et al.,* 2016a).

A significant percentage of surgical presentations such as appendicitis, cholangitis, peritonitis and osteomyelitis are associated with infections which require treatment or prevention through antibiotic prophylaxis (Leeds *et al.*, 2016). Inappropriate surgical prophylaxis can contribute significantly to the development of resistance. The Surgical Infection Society and the World Society of Emergency Surgery have encouraged surgeons to actively participate in AMS programmes (Sartelli *et al.*, 2016b). Surgeons are required to update their knowledge with the current local surgical prophylactic guidelines for surgical operations they routinely conduct and apply appropriate antibiotic treatment options in case complications ensue. They are also encouraged to work with AMS teams (Leeds *et al.*, 2016).

1.1.3 **Problem statement**

AMR is a major global problem affecting public health, especially in developing African countries where data on the degree and surveillance of resistant organisms are lacking (WHO, 2014). Globally, around 700,000 people die every year because of difficult to treat bacterial infections (O'Neill, 2016). Thus, there is an urgent need to develop programmes to address emerging drug resistant pathogens. Despite the intensified global campaign by infectious diseases physicians and other stakeholders, on the need of the hospitals to implement AMS programmes and to limit the burden of AMR, the uptake by hospitals has been erratic (Rawson *et al.*, 2015). In South Africa, there have been a limited number of AMS studies conducted in public hospitals especially in the surgical setting. An AMS programme has not been officially implemented in the Surgery Department at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), hence the need to conduct such a study. A systematic Cochrane review showed that an AMS programme can reduce AMR and improve rational antibiotic utilisation among hospitalised patients (Davey *et al.*, 2017). The

findings of this study will provide the hospital with research data that will support recommendations for rational antimicrobial utilisation and cost-effective of antibiotic therapy.

1.1.4 Rationale for the study

The need for AMS in the Surgery Department was identified because of the large volume of antibiotics use in the department. A series of meetings were held at CMJAH with representatives from the surgery department, a microbiologist from the National Health Laboratory Health Services (NHLS), pharmacists, myself and my supervisors prior to commencement of the study. During these meetings, it was established that there was no formal AMS policy and no antibiotic policy was implemented in the department. A provisional AMS team was identified, and two wards with high antibiotic utilisation in the surgery department were selected for the study. An AMS policy as determined by the South African Antibiotic Stewardship Programme (SAASP) was adopted in this study to guide the intervention process and was recommended to the department.

1.2 AIM OF THE STUDY

The aim of this study was to describe the current practice in antibiotic utilisation and measure the impact of an AMS intervention on cost and usage in selected surgical wards of the Charlotte Maxeke Johannesburg Academic Hospital.

1.3 RESEARCH OBJECTIVES

The objectives of this study are as follows:

1. To determine the impact of the introduction of an AMS policy on antibiotic utilisation by carrying out AMS rounds in two surgery wards.
2. To determine the appropriateness of antibiotic prescribing in the selected surgery wards using the guideline developed by Gyssens and colleagues (Plenat *et al.,* 1992).
3. To determine the cost impact of the introduction of this AMS intervention on antibiotic utilisation.

1.4 STUDY DESIGN

This is a quantitative study of patient records combining a prevalence cross-sectional observational and descriptive study with an interventional study. The study is divided into two stages; in the first stage the data was collected retrospectively from patient records, and in the second stage it was collected prospectively following an AMS intervention.

1.5 HYPOTHESIS

The hypothesis in this research study was that the introduction of an AMS programme will result in an improvement in appropriateness of antibiotic utilisation and reduction of consumption and cost of antibiotics.

Null Hypothesis (H_0) – that there is no difference in antibiotic utilisation, consumption or cost between the baseline cohort and intervention cohort. This study aims to reject the Null hypothesis

The Alternate hypothesis (H_A) – is that there is a difference in antibiotic utilisation, consumption or cost between the baseline cohort and intervention cohort.

CHAPTER TWO: LITERATURE REVIEW

2.1 OVERVIEW OF ANTIBIOTIC RESISTANCE

The discovery of antibiotics about seven decades ago has considerably transformed modern medicine by playing a pivotal role in the fight against infectious diseases and decreasing mortality caused by bacterial infections (Anand *et al.,* 2016; Barlam *et al.,* 2016). The rapid development of resistance by bacteria to available antibacterial agents and slow pace of research and development of new agents over the years is negatively affecting this initial success (Barlam *et al.,* 2016). Over the years, the research community has discovered over 5000 novel agents with antimicrobial activity. However, only about 100 are used clinically for managing infectious diseases (Khardori, 2006).

The first antibiotic to be discovered was penicillin in 1928 by Alexander Fleming (Kimang'a, 2012) following an accidental contamination of an agar plate by a mould (Paskovaty *et al.*, 2005) in his laboratory at St Mary's Hospital London (O'Neill, 2014). Penicillin was first administered to humans in 1941 (Grossman, 2008). A considerable quantity of antibiotics was shipped to North Africa for use by the United States army in 1943 (Kimang'a, 2012) and these played a critical role in managing infections during the Second World War (Sykes, 2001). Since their introduction into modern medicine in the 1940's, antibiotic use has widened from managing severe infections in surgical patients to the prevention of infections in patients on cancer therapy, in immunocompromised individuals and those undergoing organ transplantation as well as many other clinical indications (Gelband *et al.,* 2015). Antibiotics are also used widely as treatment, growth promoters and prophylaxis in livestock and farm animals (Laxminarayan *et al.,* 2016; Gelband *et al.,* 2015). The recent increase in the rate of AMR is alarming considering the slow pace of the discovery of new antibacterial agents in contrast with increased use in both humans and animals worldwide (O'Neill, 2014).

Antibiotic resistance is a direct function of antibiotic usage, the higher the volume of antibiotics consumed the greater the chances of developing resistance by bacteria as a mechanism of survival, in line with the Darwinian

theory of natural selection (Gelband *et al.,* 2015). Pressure from patients, especially those on medical insurance, to be treated with newer high cost agents and the high commercial demand for animal proteins are driving pressures that have resulted in increased antibiotic consumption (Gelband *et al.,* 2015). Chemotherapy, especially with cytotoxic agents, is associated with suppression of the immune system, thereby making patients vulnerable to infections, which in the absence of effective antimicrobial agents to treat or prevents such infections, increases the risk of chemotherapy (O'Neill, 2014). Similarly, without effective antibiotics, it would be risky to undertake many surgical procedures (O'Neill, 2014). Shortly after his Nobel Prize award for discovering penicillin in 1945, Prof Fleming warned that bacteria would develop resistance to these novel agents if they were not judiciously used (Paphitou, 2013; WHO, 2014).

Prof Fleming on June 26, 1945 said *"…the microbes are educated to resist penicillin, and a host of penicillin-fast organisms is bred out… In such cases the thoughtless person playing with penicillin is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope this evil can be averted" (Fishman,* 2012*).*

Nearly three years after the warning by Prof Fleming about 38% of *Staphylococcus aureus* strains were found to be resistant to penicillin in a London hospital (Huttner *et al.,* 2013; Paskovaty *et al.,* 2005). In 2008, the former United Kingdom Chief Medical Officer Sir Donaldson made the following remarks on antibiotic resistance *"Every antibiotic expected by a patient, every unnecessary prescription written by a doctor, every uncompleted course of antibiotics, and every inappropriate or unnecessary use in animals or agriculture is potentially signing a death warrant for a future patient"* (Donaldson, 2009). Similarly, the present United Kingdom Chief Medical Officer Davies in her annual report described AMR as a *"ticking time-bomb"* about to explode, requiring international attention like that given to global warming (Davies, 2013).

The percentage of prescriptions containing antibiotics per visit in developing countries is high, with about 58% in an Ethiopian teaching hospital (Desalegn, 2013), 48.43% in rural health centres of western China (Dong *et al.,* 2008) and

54.8% in Lagos, Nigeria (Odusanya, 2005), compared to 15.3% in the USA (Roumie *et al.,* 2005). A study conducted in two South African provinces, the Western Cape and Limpopo, found a high level of antibiotic use of about 68.1% in government hospitals and 31.9% of surgical cases in private hospitals. This is likely due to the high prevalence of tuberculosis and HIV-associated opportunistic infections in these regions, and lack of prescriber's knowledge on the rational use of antibiotics (Mohlala *et al.,* 2010). In 2010, a multicentre study in the USA, showed that 56% of patients had antibiotics during their inpatient stay and 30% of these patients had more than one dose of broad-spectrum antimicrobial agents (Fridkin *et al.,* 2014).

In some countries, governmental policies are contributing towards inappropriate antibiotic prescriptions. A study conducted in China between 2002 and 2005 found that some hospitals largely depend on pharmaceutical sales as their primary source of revenue, which makes up to 45% to 50% of their budget, and nearly 50% of these were from antibiotic sales (Sweidan *et al.,* 2005). Doctors have no option other than to continue prescribing antibiotics even when patients do not require them because their remuneration depends on the number of prescriptions they order (Reynolds and Mckee, 2009). In India and China some pharmacies offer incentives to prescribers who direct patients to them (Sweidan *et al.,* 2005; Laxminarayan *et al.,* 2013).

2.2 MECHANISMS OF ANTIBIOTIC RESISTANCE

Bacteria have been found to develop resistance to antibiotics using one of the following genetic strategies (Figure 2.1). Schmieder and Edwards (2012) shows that the following are the general mechanisms used by bacteria to cause resistance.

- The inactivation or modification of the antibiotic;
- An alteration in the site of the antibiotic that reduces its binding capacity;
- The modification of metabolic pathways to circumvent the antibiotic effect;
- The reduced intracellular antibiotic accumulation by decreasing permeability and/or increasing active efflux of the antibiotic;

β- lactamases cause resistance to β- lactam antibiotics via alteration in the target site of the antibiotics. The three mechanisms of β- lactam resistance are

reduced access to the penicillin-binding proteins (PBPs), reduced PBP binding affinity, and destruction through expression of β- lactamases (Rice, 2012). Figure 2.1 shows how bacteria develop resistance to different classes of antibiotics. This has all accumulated in the high percentage of resistance to antibiotics via several mechanisms in various bacterial strains (Schmieder and Edwards, 2012).

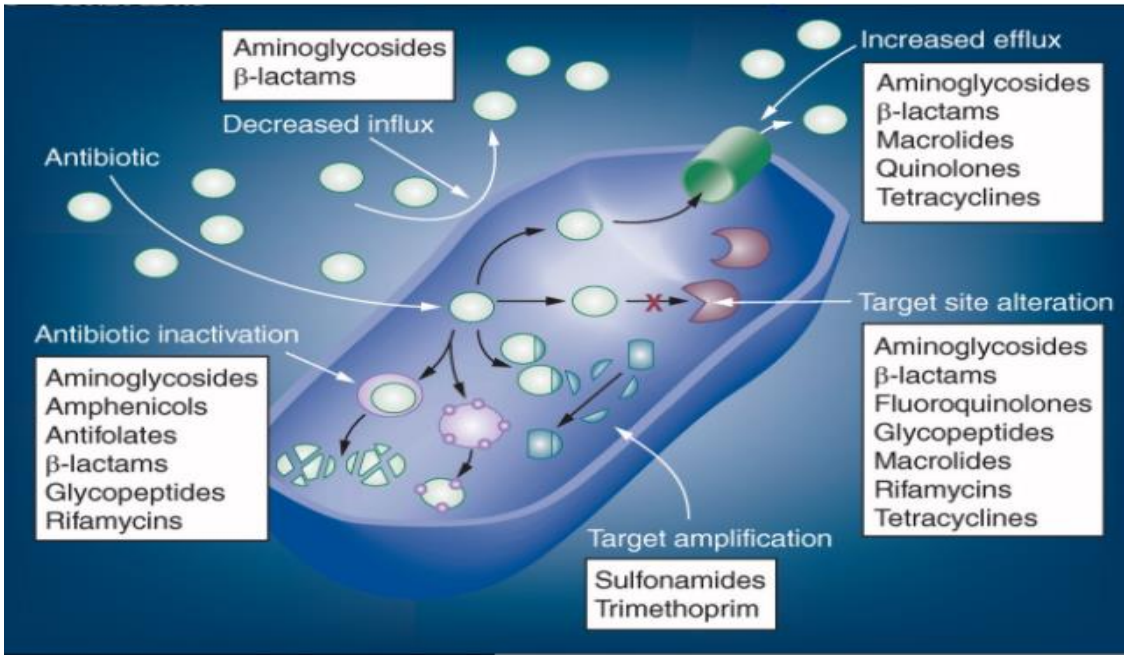

Figure 2.1: Illustration of antibiotic resistance (Schmieder and Edwards, 2012).

2.3 DRIVERS OF ANTIBIOTIC RESISTANCE

There are several factors that drive resistance to antibiotics and these include:

2.3.1 Inappropriate antibiotic use

This refers to the use of antibiotics either in the absence of bacterial infections or without indication for prophylaxis. For instance, the use of antibiotics for treating viral upper respiratory tract infections or suboptimal treatment of infections with inadequate drug dosage, incorrect route of delivery or poor adherence to the prescribed medications (Starrels *et al.,* 2009). A 2015 survey conducted by the World Health Organisation (WHO) in twelve countries revealed that 64% of the participants thought that antibiotics could be used in the management of disease conditions caused by viruses (World Economic Forum, 2015). The global community needs to do something to bridge this elementary gap of knowledge (World Economic Forum, 2015). It has been

shown that over 50% of antibiotic use in humans is inappropriate (Paskovaty *et al.,* 2005). Both appropriate and inappropriate antibiotic use drives pressure for resistance, further worsened by widespread abuse facilitated by easy accessibility over the counter without a prescription in many countries (O'Neill, 2014; Okeke *et al.,* 2005). Of note, while antibiotic therapy impacts positively only on patients who received them appropriately, the resistance developed because of their irrational usage will affect the entire community (Coulter *et al.*, 2015; World Economic Forum, 2013). Based on the findings of a study conducted between 2009 and 2010 in six USA hospitals, it was found that only 59% of the patients had a culture before the commencement of antibiotics. It further showed that up to 66% of antibiotic prescriptions were not de-escalated by the fifth day of treatment despite negative cultures in 58% of the cases (Braykov *et al.,* 2014). Also, a study conducted to assess the antibiotic utilisation in South African Intensive Care Units (ICUs), found the percentage of inappropriate antibiotic usage to be 43.5% and 60.8% in public and private ICUs, respectively, with all patients receiving an average of three antibiotics (Paruk *et al.,* 2012). The percentage of inappropriate duration of antibiotic use was also found to be 53.2% and 81.7% in public and private hospitals, respectively (Paruk *et al.,* 2012).

2.3.2 Use of broad-spectrum antibiotics

Broad-spectrum antibiotics are often used empirically to treat infections before culture results and this is associated with the development of resistance and toxicity especially when used for a long period (Pogue *et al.*, 2015). Treatment of infections with broad-spectrum classes of antibiotics are strongly linked to the emergence of resistant pathogens like methicillin-resistant *Staphylococcus aureus* (MRSA), Vancomycin-resistant *Enterococci* (VRE), *C. difficile* and multidrug resistant Gram-negative bacteria (SARI, 2009). In Canada, a relationship between a decrease in the susceptibility to fluoroquinolones among *pneumococci* and an increase in the number of prescriptions was observed. Almost all the strains of *Streptococcus pneumoniae* were susceptible to ciprofloxacin in 1988 when the prescription rate was 0.8 per 100 persons, but by 1998 about 1.7% of *S. pneumoniae* strains showed a decreased susceptibility to ciprofloxacin when its prescription rate had increased to 5.5 per 100 persons (Fishman, 2006).

2.3.3 Self-medication

Kotwani and Holloway (2011) reported that about 80% of all antibiotics are used outside the hospital setting, and most of the medicines purchased by patients in the community are without prescription especially in Low and Middle-Income Countries (Gelband *et al.,* 2015). In countries, such as Nigeria, the high use of self-medication is due to the availability of these drugs without a prescription in pharmacies (Olayemi *et al.,* 2010). The use of antibiotics without prescription outside of Europe and United States varies from 19% to 100% depending on their accessibility in the community (Morgan *et al.,* 2011). The purchase of antibiotics without prescription in Saudi Arabia is estimated to be 77.6% and less than 23% of pharmacists care to ask questions about the status of pregnancy before dispensing antibiotics in suspected cases of a urinary tract infections (UTI) (Abdulhak *et al.,* 2011). In Syria, the percentage of sales of antibiotics without a prescription is up to 87% to 97%, and this is mostly seen in Damascus the Syrian capital (Al-Faham *et al.,* 2011). Similarly, in a survey conducted in Vietnam in 2010, about 88% and 91% of urban and rural pharmacies, respectively, dispensed antibiotics without prescription (Do Thi *et al.,* 2014).

2.3.4 Antibiotics use in agriculture and environment

Antibiotics are mainly employed in agriculture to treat and prevent infections or as growth promoters in farm animals and livestock (Gelband *et al.,* 2015). The volume of antibiotic use in the agricultural sector is greater than the amount used by the human population (Gelband *et al.,* 2015). A survey conducted in the USA showed that over 80% of the total antibiotic consumption is in farm animals (Gelband *et al.,* 2015). Indiscriminate and misguided use of antimicrobial agents as growth promoters, in the treatment of infections, metaphylaxis and prophylaxis among farm animals, in livestock as well as in aquaculture has also significantly contributed to the spread of resistant strains to humans through direct contact and via environmental contamination (Roca *et al.,* 2015). Colistin (Polymyxin E) is one of the few cationic antimicrobial peptides used in both human and as a growth promoter in veterinary medicine (Rhouma *et al.*, 2016). For several years now, colistin has been considered the last line of defence against infections caused by multidrug resistant Gram-negative bacteria such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and

Klebsiella pneumonia (Rhouma *et al.*, 2016). To prevent cross-resistance, the WHO in 2005 identified antimicrobial agents that are crucial for human health and made a recommendation to restrict their uses for nonhuman purposes some of which include; tigecycline, carbapenems and daptomycin (WHO, 2011b).

Antibiotic consumption in farm animals is predicted to increase in coming years in response to the need for meat and dairy products which is expected to double by 2050 due to the projected increase in human population from 7 billion at present to 9 to 10 billion in the next 35 years (Gelband *et al.,* 2015). An estimated 63,151 tons of antibiotics were used on livestock in 2010 worldwide (Van Boeckel *et al.*, 2015) amounting to two-thirds of the global 100,000 tons of antibiotics produced (Bbosa and Mwebaza, 2013). Antibiotic consumption in farm animals is predicted to increase by 67% i.e. 105,600 tons by 2030 (Van Boeckel *et al.,* 2015). Similarly, use in the Brazil, Russia, India, China and South Africa (BRICS) countries is expected to double by 2030 (Van Boeckel *et al.,* 2015). Even in countries like the United Kingdom where there are established laws regulating the use of antibiotics for agricultural purposes, nearly 387 tons of antibiotics were utilised for farming activities in 2007 (Donaldson, 2009). Similarly, in 2010 in the USA about 13,000 tons of antibiotics were used on animals mostly as growth enhancers (Spellberg *et al.,* 2013). A study to determine the volume of antibiotics consumed by farm animals in South Africa between 2002 and 2004, has found a high level of consumption where more than 1,538 tons were consumed mostly in feeds (Eagar *et al.*, 2012). Macrolides and pleuromutilins were the most commonly used classes, followed by tetracyclines, sulphonamide and penicillin (Eagar *et al.*, 2012).

Price *et al.* (2007) found that the incidence of drug-resistant bacteria in the gastro-intestinal tract is higher in individuals who work on farms that use antibiotics as growth promoters than those who work on farms that do not use them. Also, there is a 32-fold higher chance of contracting a gentamycin-resistant *E. coli* infection in workers that work on such farms than the general public (Price *et al.,* 2007). To further contribute to the development of resistance, excreted antibiotic residues by both humans and animals through

urine and faeces will find their ways into the environment (Daghrir and Drogui, 2013). Some of these residues disintegrate in the environment, while others may withstand treatment chemicals in water processing plants, therefore selecting pressure for resistance (Gelband *et al.,* 2015). A study conducted in the United Kingdom has found the presence of genes encoding resistance to certain antimicrobial agents such as sulphonamide, tetracyclines and trimethoprim in rivers that receive waste materials from farms and water treatment plants (Rowe *et al.,* 2016).

Similarly, researchers in India and Bangladesh have identified a significant number of enzymes, such as New Delhi Metallo-beta-lactamase-1 (NDM-1) and Cefotaximase-Munich-15 that confer resistance to some broad-spectrum antibacterial agents in municipal water supplies and the environment (Rashid *et al.,* 2015; Toleman *et al.,* 2015; Walsh *et al.,* 2011). The use of bioengineering technologies in the treatment of sewage helps to disintegrate these antibiotics and their residues, thereby reducing the chances of selecting resistant bacteria in the environment (Spellberg *et al.,* 2013). If preventive measures such as vaccination, farm hygiene and cross breeding are used, they will go a long way in reducing the demand for antibiotics in treating infections and growth promotion in farm animals (Gelband *et al.,* 2015). Figure 2.2 shows how man, animals and environment relate in the development of AMR.

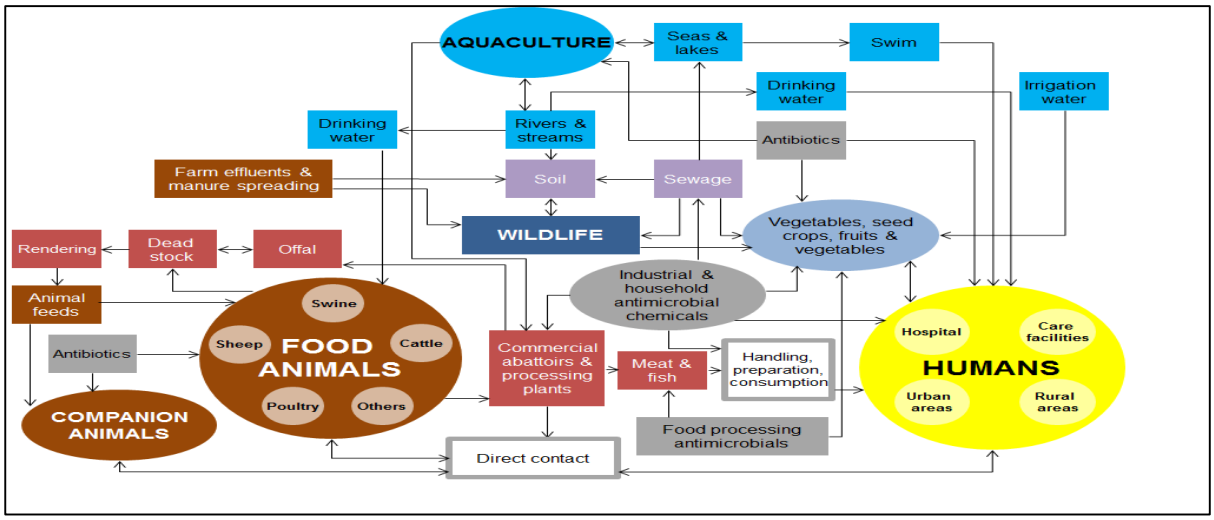

Figure 2.2: Interaction between antimicrobial use in man, animals and environment [Based on Linton (1977), as adapted by Rebecca Irwin, Health Canada (Prescott 2000) and IFT].

2.3.5 **Counterfeit drugs**

The use of counterfeit antibiotics is associated with the development of AMR, increased morbidity and mortality (Kelesidis *et al.*, 2007). WHO held a joint workshop in 1992 with the International Federation of Pharmaceutical Manufacturers Association on the negative public health impact of substandard drugs. This forum adopted the definition of counterfeit drugs as *"One which is deliberately and fraudulently mislabelled on identity and/or source. Counterfeiting can apply to both branded and generic products, and counterfeit products may include products with the correct ingredients or wrong ingredients, without active ingredients with an insufficient active ingredient or fake packaging." (WHO,* 1999*).*

As stated in a report by the WHO and Food and Drug Administration (FDA) nearly 10% of drugs in the global market are counterfeit and even more alarming is that this figure may be more than 30% in developing countries (Pincock, 2003; Rudolf, 2004). In Africa and Asia up to 60% of antimicrobial agents have been reported to be substandard (Kelesidis and Falagas, 2015; Nayyar *et al.,* 2015). Nigeria is one of the African countries reported to have over 70% counterfeit drugs in circulation with most of these substandard drugs imported from India, China, Pakistan, Egypt and Indonesia (Raufu, 2002; Raufu, 2003).

2.4 **BACTERIA OF GLOBAL CONCERN**

The bacteria of global concern are the ESCAPE pathogens and these are *Enterococcus* (VRE), *Staphylococcus* (MRSA, VRSA, hVISA), *and C. difficile*/*Candida* spp, *Acinetobacter*, *Pseudomonas* and *Enterobacteriaceae* (including *Klebsiella*, *E. coli*, *Serratia* and *Proteus*) (Richard G, presented during AMS workshop at CMJAH, 2016). These are similar to ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter* species) as referred by IDSA (IDSA, 2010). The resistance of *E. coli* to fluoroquinolones and third generation cephalosporins has been estimated to be over 50% in five of the six WHO regions (WHO, 2014). The rate of *K. pneumoniae* resistance to third generation cephalosporins is over 30% in many of the WHO member countries and above 60% in some parts (WHO, 2014). Between 2011 and 2014 England reported an increase in the prevalence of *E.*

coli and *K. pneumoniae* bloodstream infections by 15.6% and 20.8%, respectively, compared with a 23% reduction in bloodstream infections caused by *S. pneumoniae* probably due to pneumococcal vaccination (Ashiru-Oredope and Hopkins, 2015). As reported by Johnson *et al.* (2012) the resistance of *S. aureus* to penicillin in the United Kingdom and in parts of the USA is presently estimated at 90%. Resistance may develop to penicillin, and in some regions in the USA, 50% of its strains are resistant to methicillin (Klevens *et al.,* 2007). In Africa, resistance patterns in methicillin-sensitive *Staphylococcus aureus* (MSSA) is high in urban areas which is around 73.7% to 100% for penicillin, 15% to 89.1% for co-trimoxazole and 21.8% to 92% tetracycline compared to remote regions where the resistance rate is around 35.3% penicillin, 11.8% co-trimoxazole and 5.8% for tetracycline (Schaumburg *et al.,* 2014). A study conducted in surgical wards and the ICU of a Greek hospital found *S. aureus* to be the most frequent bacteria causing SSIs (Călina *et al.*, 2017). It was highly resistant to first-and second-line antibiotics, such as, ceftriaxone (100%), penicillin (91.4%), amoxicillin/clavulanic acid (87.5%) and amikacin (80.0%) (Călina *et al.*, 2017). The resistance of MRSA was found to be above 20% in all the WHO regions and in some areas, it exceeded 80% (WHO, 2014). The South African National Department of Health (NDoH) reported an outbreak of *Klebsiella pneumoniae* bacteria in 2011 which was resistant to all available antibacterial agents except colistin which was not licensed for use in South Africa at the time (NDoH, 2014a). An increase in intercontinental travel, especially for medical tourism, facilitates the smooth spread of drug-resistant pathogens globally (O'Neill, 2014). This mixing of different pathogens facilitates the rapid development of new resistant strains (O'Neill, 2014). Most of the cases of hospital acquired infections are caused by these bacteria (Rice, 2008). Some bacteria causing bacterial infections in hospitals include the following listed below:

2.4.1 ***Acinetobacter baumannii***

This is a Gram-negative bacterium causing a broad range of infections such as nosocomial bloodstream infections and pneumonia and has been found to be highly resistant to beta-lactams and fluoroquinolones (Kim *et al.,* 2014). It causes resistance by pumping drugs out of the cell via the porin-efflux pump

(Cag *et al.,* 2016). Other ways it causes resistance are via antimicrobial inactivating enzymes, reduced access to bacterial targets, or mutations that changes targets or cellular functions. It also produces carbapenemases and uses combinations of AMPc and porin mediated resistance (Eliopoulos *et al.*, 2008). In China, more than 60% of *A. baumannii* are resistant to carbapenems (Fupin *et al.,* 2014). Sentinel surveys in South African public hospitals show it is resistant to most antibiotics. Rates of resistance to some of those drugs tested include imipenem 77%, colistin 5%, cefepime 79% and ceftazidime 75% (Perovic *et al.,* 2014). Colistin is regarded as the drug of choice in treating carbapenem-resistant *A. baumannii*, although its resistance is reported globally especially in Europe and Asia (Cai *et al.,* 2012).

2.4.2 *Pseudomonas aeruginosa*

This Gram-negative pathogen causes resistance similar *to Acinetobacter baumannii* by pumping drugs out of the cell via the porin-efflux pump (Cag *et al.,* 2016). Other ways include; antimicrobial inactivating enzymes, reduced access to bacterial targets, or mutations that change targets or cellular functions. It also produces carbapenemases and uses combinations of AMPc and porin mediated resistance (Eliopoulos *et al.*, 2008). A recent study in the USA identified a certain strain of *P. aeruginosa* that was resistant to ceftazidime/avibactam, and ceftolozane/tazobactam - newly approved by the FDA for treating *P. aeruginosa* (Gangcuangco *et al.,* 2016). In South African public hospitals, it is less resistant than *A. baumannii,* with 33% resistance to piperacillin/tazobactam and rare resistance to colistin (Perovic *et al.,* 2014). Piperacillin/tazobactam, ciprofloxacin, aminoglycoside or cefepime are empirically recommended by the SAASP in treating suspected infections caused by *P. aeruginosa* before culture results are available (Wasserman *et al.,* 2014).

2.4.3 *Enterococcus faecium*

Enterococcus faecium causes resistance via enzymatic degradation (Giedraitienė *et al.*, 2011). It is intrinsically resistant to penicillin and cephalosporin and low concentrations of aminoglycosides (Perovic *et al.,* 2014). Resistance to vancomycin decreased from 13% to 5% between 2013 and 2014 in South Africa probably because of an improvement in infection control in some

hospitals (Perovic *et al.,* 2014). Vancomycin is empirically recommended by the SAASP as a drug of choice for treating suspected infections caused by *E. faecium* while waiting for culture results (Wasserman *et al.,* 2014).

2.4.4 *Escherichia coli*

A plasmid-mediated resistant gene transfer is the primary mode of resistance operated by *E. coli* with a minor contribution from the porin-efflux system (Cag *et al.,* 2016). In Europe, 17 of 22 countries reported 80% to 100% of isolated *E. coli* were ESBL-producers (EARS-Net, 2014). Sentinel surveys in South African public hospitals found a small rise in resistance to the beta-lactam class of antibiotics without a considerable increase in ciprofloxacin resistance (Perovic *et al.,* 2014). The SAASP recommends the use amoxicillin/clavulanic acid, ceftriaxone, aminoglycosides and ciprofloxacin to treat community acquired UTIs caused by *E. coli* (Wasserman *et al.,* 2014). Carbapenems such as ertapenem are the drug of choice in cases of ESBL- producing *E. coli* and *Klebsiella* spp (Van Aken *et al.*, 2014; Wasserman *et al.,* 2014). The most appropriate antibiotic to treat carbapenem-resistant *Enterobacteriaceae* (CRE), related sepsis is still debatable, however, combination therapy is preferred to monotherapy (Alhashem *et al.*, 2017). In severely ill patients with co-morbidities a combination of two or more antibiotics is preferred. One of the most commonly used combinations until recently was meropenem, tigecycline and colistin. However, a second option to be considered is tigecycline, gentamycin and meropenem (Alhashem *et al.*, 2017).

2.4.5 *Klebsiella pneumoniae*

Klebsiella pneumoniae is the primary Gram-negative bacterium causing infections in Africa and Asia and it is responsible for almost half of all Gram-negative infections in neonates (Le Doare *et al.,* 2015). The rate of resistance of *K. pneumoniae* to ampicillin and cephalosporins in Africa is up to 100% and 50%, respectively, and in Asia it is around 94% and 84%, respectively (Le Doare *et al.,* 2015). There was a steep increase in the rate of resistance of *K. pneumoniae* to carbapenems reported in Indian tertiary health care centres from 2% in 2002 to 52% in 2009 in New Delhi (Datta *et al.,* 2012). Blood analysis of inpatients from 2010 to 2012 in South Africa showed that 75% of *K. pneumoniae* infections were ESBL-producers (Mendelson, 2015b). In 2008, doctors in

Sweden diagnosed a man from India who developed a UTI, which was resistant to all antibacterial agents except colistin (Moellering, 2010). The infection was caused by *K. pneumoniae* carrying a gene encoding NDM-1 which rapidly spread across the globe within a few years (Moellering, 2010). The first case of *K. pneumoniae* carrying the gene encoding NDM-1 in Africa was reported in Kenya in 2009 (Poirel *et al.,* 2011). NDM-1 *K. pneumoniae* was isolated in both South African public and private hospitals in 2011 (Brink *et al.,* 2012; Lowman *et al.,* 2011). NDM-1's are carbapenemases which are β- lactamases enzymes with an ability to hydrolyse not only the carbapenems but also all other β- lactam agents (Perovic *et al.*, 2016). Other carbapenemases include veronica integron metallo-beta-lactamases type (VIM), imipenemases (IMP), *Klebsiella pneumoniae* carbapenemase (KPC), and oxacillinase-48 (OXA-48) (Okoche *et al.*, 2015). A 4 year study in South Africa showed that the most common carbapenemase-producing genes were $^{bla}_{NDM}$ (59%), $^{bla}_{OXA\text{-}48}$ (29%), $^{bla}_{VIM}$ (7%), $^{bla}_{IMP}$ (2%), $^{bla}_{GES}$ (1%) and $^{bla}_{KPC}$ (1%) (Perovic *et al.*, 2016). Amoxicillin/clavulanic acid, ceftriaxone, ciprofloxacin or aminoglycoside are empirically recommended by the SAASP in treating suspected infections caused by *K. pneumoniae* before culture results (Wasserman *et al.,* 2014).

2.4.6 *Enterobacter cloacae*

It is an *enterobacteriaceae* which produces enzymes that are EBLS in nature and there is a global increase in IMP-Producing *Enterobacter cloacae* among carbapenemase-producing *Enterobacteriaceae* (Sidjabat *et al.*, 2015). It causes resistance to antibiotics via enzymatic degradation (Giedraitienė *et al.*, 2011). It's resistant rates to imipenem and meropenem in South African public hospitals have been reported at 2% with cefepime resistance noted at 35% (Perovic *et al.,* 2014). The SAASP has recommended the use of ciprofloxacin, aminoglycoside or cefepime empirically in suspected infections caused by *E. cloacae* before culture results (Wasserman *et al.,* 2014).

2.4.7 **Methicillin-resistant *Staphylococcus aureus***

MRSA was previously limited to the hospital environment, but recently it has been associated with community-acquired infections associated with skin and soft tissue infections, pneumonia and severe blood stream infections (Gelband

et al., 2015). Sub-Saharan African countries have witnessed a sharp increase in MRSA prevalence since the beginning of the 2000s (Gelband *et al.,* 2015). However, in South African referral hospitals it has been demonstrated that it's prevalence has decreased from 36% in 2006 to 24% during 2007 to 2011, because of the implementation of effective infection control policies (Kariuki and Dougan, 2014). Bamford *et al.* (2011) reported that MRSA was 30% to 60% resistant to cloxacillin in South Africa. Similarly, reports from Europe and the USA showed a reduction in MRSA over the past eight years from 22% to 18% and from 53% to 44%, respectively (Gelband *et al.,* 2015). Conversely, in some developing countries like India, there has been a sudden increase in MRSA prevalence from 29% of *S. aureus* isolates in 2009 to 47% in 2014 (Gelband *et al.,* 2015). MRSA is responsible for over 10% of blood stream infections in 15 European countries (Gelband *et al.,* 2015). In South Africa about 75% of nosocomial *S. aureus* infections in tertiary paediatric hospitals are caused by MRSA (Gelband *et al.,* 2015). Similarly, positive blood cultures from nosocomial *S. aureus* infections were caused by MRSA in more than half of patients in other public sector hospitals (Mendelson, 2015b). Sentinel surveys in South African public hospitals show that MRSA is 41% resistant to cefoxitin and 20% to 35% resistant to lincosamides and macrolides (Perovic *et al.,* 2014). The SAASP has recommended the use of cloxacillin and vancomycin as drugs of choice for treating MSSA and MRSA, respectively (Wasserman *et al.,* 2014).

2.4.8 **Extended spectrum beta-lactamase producers**

ESBLs are Gram-negative bacteria that produce enzymes which resist the most commonly used antibiotics (Reuland *et al.,* 2014; WHO, 2014). ESBLs inactivate all penicillins and cephalosporins (Gelband *et al.,* 2015). As stated by Leopold *et al.* (2014) resistance patterns of ESBLs to third generation cephalosporins in sub-Saharan Africa vary from one country to another, with a wide range of resistance from 0% to 47%. In South African hospitals rates range from 0.3% – 13.1% in some communities (Storberg, 2014). ESBL Gram-negative bacteria commonly cause hospital-acquired UTIs with resistance to first-line antibiotics, necessitating the use of more expensive second-line antibiotics (Mendelson, 2015a). In West African United Nation, = sub-regions, the prevalence of ESBLs ranges from 10% to 96% of community samples (Storberg, 2014). In Maiduguri, north-eastern Nigeria 33.5% of *K. pneumoniae*

and *E. coli* isolates were found to be ESBL producers, but only 23.6% were positive on the double disk synergy technique (Mohammed *et al.,* 2016). In North African countries, ESBL prevalence ranges from 11% to 78% in hospitals and 1% to 8% in the communities (Storberg, 2014). In East Africa, ESBLs were found in 38% to 63% of hospitals samples and 6% of population samples (Storberg, 2014). In Central Africa, 55% to 83% of hospital samples were ESBL-positive and rates of 11% to 17% were noted in the community (Storberg, 2014).

2.4.9 Carbapenem-resistant *Enterobacteriaceae*

While a report from hospitals in developed countries has shown an increased infection rate caused by CRE (Lerner *et al.,* 2014), a similar pattern has also been reported in developing countries (Gelband *et al.,* 2015). In 2012, about 11% of *Klebsiella* spp and 2% of *E. coli* were resistant to carbapenems in the USA (Gelband *et al.,* 2015). In 2015, there was an outbreak of carbapenem-resistant *Providencia rettgeri* among patients in an ICU of a tertiary South African hospital, with one of them developing the infection after abdominal and pelvic procedures required to treat gunshot injuries (Tshisevhe *et al.*, 2016).

2.4.10 *Clostridium difficile*

Treatment of infections with antimicrobial agents either appropriately or inappropriately changes the equilibrium of intestinal microflora by destroying bacterial volume, thereby creating an enabling environment for *C. difficile* to proliferate (CDC, 2013; Mcdonald *et al.,* 2012). These infections can be fatal especially in individuals with compromised immunity and in the elderly (Fridkin *et al.,* 2014). Treatment of infections with broad-spectrum antibiotics such as third generation cephalosporins, clindamycin and fluoroquinolone are associated with the development of *C. difficile* infection, with about US$ 8 billion spent annually in the treatment of diseases associated with *C. difficile* in the USA (Owens *et al.,* 2008), especially with chronic antibiotic therapy. The annual incidence of *C. difficile* infection was about 8.7 cases per 100,000 admissions in a South African tertiary hospital, and one-third of these infections were community acquired, this is below the annual incidence of western countries of about 74 cases per 100,000 admissions (Rajabally *et al.,* 2013). According to Onwueme *et al.* (2011) in Nigeria, the prevalence of *C. difficile* in HIV-positive individuals was 43% among hospitalised cases and 14% among outpatients

with diarrhoea. It was responsible for 250,000 cases and up to 14,000 mortalities in the USA (CDC, 2013). It has been reported that there is a 7 to 10-fold increase in the chance of acquiring a *C. difficile* infection after a month of discontinuing antibiotics treatment (Brown *et al.,* 2015; Hensgens *et al.,* 2012). AMS programmes have been shown to reduce the likelihood of developing *C. difficile* infections by 52% (Feazel *et al.,* 2014). The SAASP has recommended metronidazole and oral vancomycin as the drugs of choice in the treatment of infection caused by *C. difficile* (Wasserman *et al.,* 2014).

2.4.11 **Vancomycin-resistant *Enterococci***

Vancomycin-resistant *Enterococci* (VRE) were first discovered in 1987 in Europe and within a few years they had spread globally (Willems *et al.,* 2005). In 2012, South Africa recorded an outbreak of VRE in both public and private health facilities (NDoH, 2014a). In North America, a reduction in its spread was noticed following implementation of infection control measures (Huttner *et al.,* 2013). Linezolid is empirically recommended by the SAASP as a drug of choice for treating suspected infections caused by VRE while waiting for culture results (Wasserman *et al.,* 2014).

2.5 **GLOBAL ANTIBIOTIC CONSUMPTION**

The world has witnessed a tremendous increase in the volume of antibacterial use in the last decade by over 30%, from approximately 50 billion standard units (SUs) in 2000 to 70 billion SUs in 2010. Globally, penicillin and cephalosporins are the most commonly consumed antibiotics accounting for up to 41% in 2000; with this figure steeply increasing to 60% in 2010 (Van Boeckel *et al.,* 2014). There is also an increase in the global use of last resort antibiotics such as carbapenems (45%) and polymyxins (13%) (Van Boeckel *et al.,* 2014). Some of the old antimicrobials that had lost their popularity in the past due to toxicity like colistin, are now gradually being re-introduced to treat multidrug-resistant bacterial infections (Wertheim *et al.,* 2013a). An increase of 6.7% in antibiotic consumption was noted in England from 21.6 Defined Daily Doses (DDDs) per 1000 inhabitants per day in 2011 to 23 DDDs per 1000 inhabitants per day in 2014 (Ashiru-Oredope and Hopkins, 2015). In 2010, countries like India, China and the United State were the leading consumers of antibiotics with these countries alone consuming 13 billion SUs, 10 billion SUs, and 7 billion SUs,

respectively. But in per capita terms, the United States has exceeded the other two countries, with 22 SUs per individual compared with 11 SUs and 8 SUs per individual in India and China, respectively (Van Boeckel *et al.,* 2014). A substantial increase in antibiotic utilisation has been noted in the five fastest growing economies in the world, the so-called BRICS countries, from 2000 to 2010, these countries alone accounted for three-quarters of the global consumption in 10 years (Van Boeckel *et al.,* 2014). Laxminarayan *et al.* (2016) predicted that effective pneumococcal vaccination would reduce antibiotic use by up to 11.4 million antibiotic days for treating pneumonia cases in children under five years, which is almost equivalent to a 47% decrease in the volume of antibiotics for treating pneumonia in 75 countries. Figure 2.3 shows the world economic burden and impact of AMR.

2.6 EMERGENCE OF RESISTANCE TO LAST RESORT ANTIBIOTICS

A review of carbapenem-resistant bacteria across South African provinces from January 2000 to May 2016 showed that about 2,315 cases were isolated with the Gauteng province having the highest number of cases at 1,220 followed by KwaZulu-Natal with 515 (Sekyere, 2016). Most of these cases could not be linked with travel history from other countries indicating that the strains were selected due to high carbapenem consumption nationwide (Sekyere, 2016). There has been a gradual increase in isolation of these pathogens that confer resistance to last resort antibacterial agents such as carbapenems, colistin and tigecycline in South Africa (Sekyere, 2016). Of note, the recent identification of Mannose Receptor, C Type 1 (*mcr-1*) gene among *E. coli* in two provinces is a great public health concern not only in South Africa, but also in other African and European countries (Sekyere, 2016). Patients from all over Africa seek medical care in South Africa because of the quality of health facilities, while patients from Europe come to this country because of more affordable services (Crush *et al.,* 2012). Medical tourism is considered a quick way of transmitting resistant pathogens across the globe (Crush *et al.,* 2012).

Colistin is regarded as one of the last resort antibiotics for treating resistant bacterial infections (Sprenger, 2016). Even though it was discovered in 1949; its intravenous usage on humans was gradually abandoned due to its toxicity, however, it continued to be used widely in animals as a growth promoter

selecting resistant bacteria (Falagas *et al.,* 2005). But recently its usage has increased due to an increase in bacterial resistance to first- and second-line antibiotics (Sprenger, 2016). Bacteria develop resistance to colistin and tigecycline by promoting a mutation in lipid A and by pumping these drugs out of the cells via porin-efflux pumps (Osei Sekyere et al., 2016).

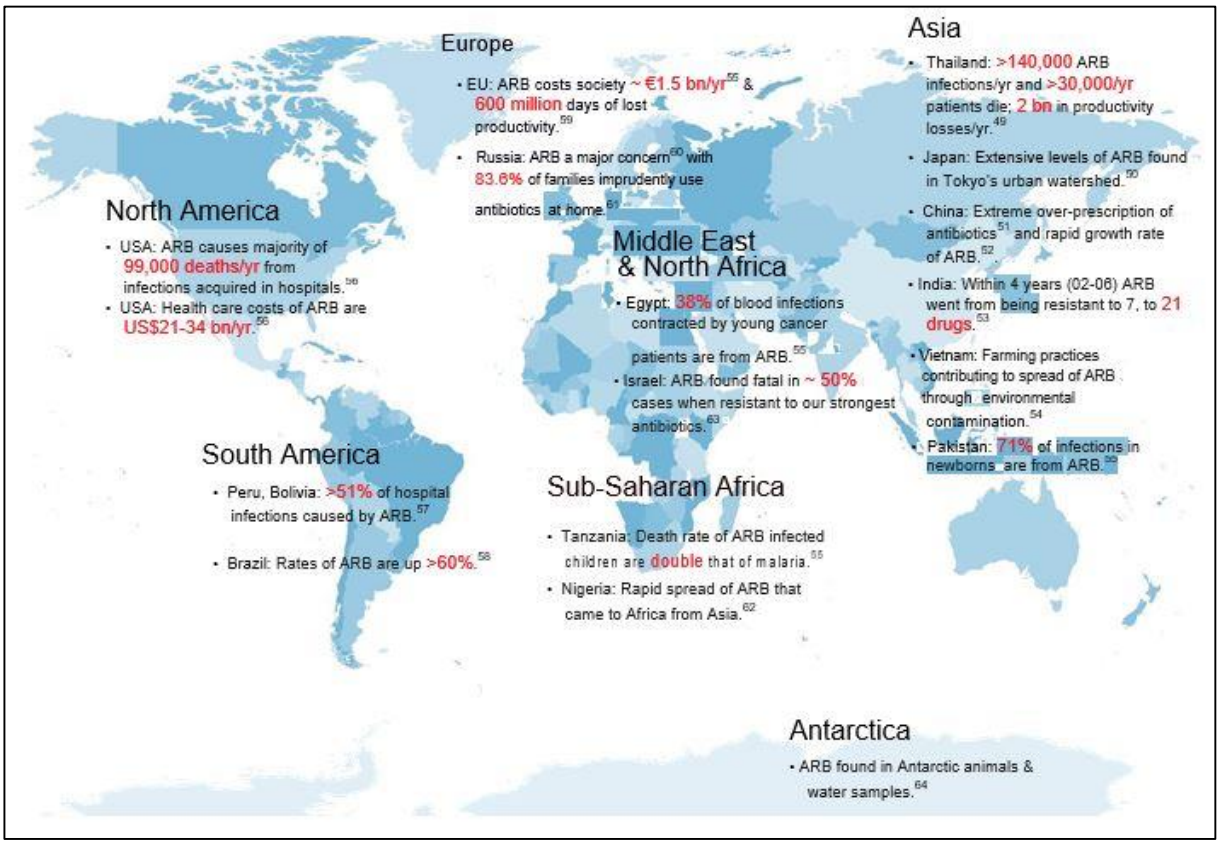

Figure 2.3: Global transmission of antimicrobial resistant bacteria (World Economic Forum, 2013).

Until recently, colistin resistance was limited to chromosomal mutation, however, in 2015 the first case of plasmid-mediated *mcr-1* resistant *Enterobacteriaceae* was identified in pigs in China which is of global concern (Liu *et al.,* 2016). Since its discovery in China, it has spread across the globe and has recently been identified in the United States in a urine specimen of a patient suffering from a UTI (Mcgann *et al.,* 2016). In South Africa, the *mrc-1* gene has been isolated from colistin- resistant strains of *E. coli* in two different Provinces namely Gauteng and Western Cape (Coetzee *et al.,* 2016).

2.7 ANTIBIOTIC PIPELINE

The pipeline to produce new classes of antibacterial agents has not been active recently leading to significant scientific bottlenecks in the development of new agents. As a result, the last time a new class of antibacterial agent was discovered was in the 1980s (WHO, 2014; Roca *et al.,* 2015). Four sets of new antibiotics from existing classes were approved by the FDA in the USA in 2014, namely dalbavancin, tedizolid, oritavancin and ceftolozane/tazobactam; and in 2015 it also licenced ceftazidime/avibactam (Doshi, 2015). Drug development is a capital-intensive business with only a small proportion of drugs that begin preclinical trials progressing through to obtain approval from stringent drug regulatory bodies such as the European Medicines Agency (EMA) and FDA (Gelband *et al.,* 2015). Antimicrobial agents provide little profit to pharmaceutical companies because they are usually prescribed for a short duration compared to other classes of medicines used for treating chronic conditions (Marston *et al.,* 2016). In addition, inexpensive generics of original products that are relatively active in certain infections are preferred as first-line drugs to preserve newer agents for life-threatening bacterial infections (Morel and Mossialos, 2010). Only a few pharmaceutical companies invest in the research and development of antimicrobial agents. These companies aggressively market their products to doctors to recover their capital investment and this may compromise the effort at preventing resistance (Donaldson, 2009).

2.8 SURVEILLANCE OF RESISTANT BACTERIA IN AFRICA

In 2014 the WHO report on AMR and surveillance indicated that there is a lack of accurate and reliable data concerning the extent of AMR in Africa, as surveillance of drug-resistant organisms is conducted in only a few countries of the region (WHO, 2014). It further noted a lack of regional collaboration in the monitoring of resistant organisms and sharing of information among the networks of laboratories in the area (Gelband *et al.,* 2015). However, high rates of resistance have been reported in many bacteria, increasing the risk of spread of resistance in both hospitals and communities in this region (Gelband *et al.,* 2015; WHO, 2014). South Africa is one of the few African countries with a good surveillance system with reliable data captured in both public and private health institutions. It has established surveillance for ESKAPE organisms (Gelband *et al.,* 2015). The data collected in public laboratories are reported to the National

Institute of Communicable Diseases and consists of data gathered from public sentinel hospitals by the group for Enteric, Respiratory and Meningeal Disease Surveillance in South Africa, a national clinical microbiology network (Gelband *et al.,* 2015). About 31 hospitals and over 200 laboratories conduct surveillance on 12 organisms (Gelband *et al.,* 2015). The South African Society of Clinical Microbiology is responsible for collating data on 13 microorganisms in five laboratory groups of private organisations. These sets of data are centrally analysed and consolidated by the South African Antibiotic Resistance Partnership and Group for Antibiotic Resistance Partnership (GARP) (Gelband *et al.,* 2015).

2.9 INFECTION CONTROL

Healthcare-associated infections refer to infections acquired by patients while being treated in hospital; they are mostly transmitted through the hands of hospital personnel, hospital equipment or contamination of surgical wounds (Cristina *et al.,* 2013; Gelband *et al.,* 2015; Pittet *et al.,* 2006). Infection control measures such as hand hygiene are shown to reduce transmission of pathogenic microorganisms from hospital personnel to patients (Boyce and Pittet, 2002). Infection-control measures also reduce sepsis (Sinha *et al.*, 2015) and decrease infections caused by MRSA (Aldeyab *et al.,* 2008). They also reduce antibiotic prophylaxis in patients with UTI by up to 2 DDDs per day (Stéphan *et al.,* 2006). Evidence from randomised controlled trials (RCTs) show that hand washing with soap and water or alcohol solution reduces hospital acquired infections (Allegranzi and Pittet, 2009; Barnett *et al.,* 2014; Pittet *et al.,* 2006). Despite these benefits, a significant percentage of health-care providers do not follow hand washing guidelines in developed countries (Erasmus *et al.*, 2010). While in developing countries lack of water, soap and understaffing are the primary barriers to hand washing (Boyce and Pittet, 2002).

2.10 SURGICAL SITE INFECTIONS

SSIs are the 3rd most common type of nosocomial infections and represent about 15% of all nosocomial infections (ECDC, 2013). Patients with SSIs have a 60% chance of ICU admission, high rate of readmission, increased hospital cost and are more likely to die compared to those who do not develop SSIs

(Brink *et. al*., 2016c). A retrospective review that measured the impact of SSIs in the 1990s on patient outcomes found that the median duration of inpatient stay was 11 days for patients who developed SSIs and 6 days for patients who did not develop SSIs (Kirkland *et al.,* 1999). The total hospital cost incurred by patients who developed SSIs was US$ 7,531 compared to US$ 3,844 incurred by those who did not have SSIs (Kirkland *et al.,* 1999). Developing countries have a higher burden of nosocomial infections compared to developed countries (Nejad *et al.,* 2011). A systematic review by the WHO in 2011 showed that there are limited studies conducted on nosocomial infections in Low and Middle Income Countries (Allegranzi *et al.,* 2011). Another review indicates that there are a limited number of interventional studies designed to address the burden of SSIs in Africa and only found 24 of such studies over 15-year period in sub-Saharan Africa (Aiken *et al.,* 2012).

SSIs are responsible for a significant proportion of hospital-acquired infections, yet many hospitals do not have information on probable risk factors for SSIs in patients undergoing an operation (Wilson, 2014). Conducting surgical operations in developing African countries is associated with serious problems ranging from shortage of skilled personnel and standard operating theatres to the high incidence of SSIs (Aiken *et al.,* 2012). Factors that causes SSIs include pathogens introduced into the operation site, the number of bacteria that remain when the wound is dressed, the ability of the pathogen to grow and invade tissues and the inability of the host's immune system to fight back (Wilson, 2014). Other factors include malnutrition, diabetes and smoking (Reichman and Greenberg, 2009).

A study conducted in southern Nigeria showed that *S. aureus* was the most common cause of SSIs, at 25%, then *P. aeruginosa* at 20%, followed by *E. coli* at 15% and *K. oxytoca* and *Proteus mirabilis* accounted for 10% each; while the coagulase-negative *Staphylococcus*, *Streptococcus pyrogenes*, *K. aerogenes* and *Proteus vulgaris* each accounted for 5% (Anthony *et al.,* 2010). Gram-positive bacteria were strongly resistant to penicillin, cloxacillin, and ampicillin except for *S. aureus* which was found to be 70% to 90% sensitive to streptomycin and erythromycin (Anthony *et al.,* 2010). Antibiotic susceptibility shows that Gram-negative bacteria were strongly resistant at 70% to 100% to

co-trimoxazole, ampicillin, streptomycin and tetracycline, but sensitive in about 70% to 90% of samples to colistin and gentamycin excluding *P. aeruginosa* and *K. oxytoca* (Anthony *et al.,* 2010). The incidence of SSIs in India varies from 4% to 30% for clean operations to 10% to 45% for clean-contaminated operations, with *S. aureus* and *P. aeruginosa* being the commonest cultured bacteria (Lilani *et al.,* 2005). Prolonged surgical procedures, drained wounds and extended hospitalisation before and after surgery were associated with high chances of contracting SSIs in India (Lilani *et al.,* 2005). SSIs increase health care cost because of additional days of admission, laboratory investigations, other antibiotic courses and increased possibility of repeat surgeries (Reichman and Greenberg, 2009). In 2009, a study showed that SSIs prolong duration of hospital admission by an average of 9.5 days with an associated cost implication of US$ 20,842/admission (De Lissovoy *et al.,* 2009). The WHO has recently adopted 29 recommendations to lessen the chances of SSIs before, during and after surgical procedures. These include: preoperative bathing, appropriate timing of surgical prophylaxis, bowel preparation, and non-shaving of hair before surgery, others are proper hand washing before scrubbing and intranasal application of mupirocin among *S. aureus* carriers undergoing orthopaedic and cardiothoracic procedures (WHO, 2016b).

Fungal infections are often neglected when evaluating patients with surgical infections, the rate of these infections after intra-abdominal procedures is rising (Soop and Carlson, 2017). A study across 97 hospitals in the United States showed that *Candida albicans* 39.6% and *Candida glabrata* 35.7% were the most common pathogens causing fungal septicaemia after intra-abdominal procedures. It further showed an increased chance of acquiring an infection with fluconazole-resistant pathogens among patients who had fluconazole prophylaxis (Zilberberg *et al.*, 2014).

2.10.1 **Classification of surgical wounds**

Surgical wounds are classified into four different types (Mangram *et al.,* 1999).

- Clean wounds: these refer to injuries that are uninfected, without inflammation. They are primarily closed under aseptic condition.
- Clean-contaminated wounds: here the surgical procedures are performed under controlled techniques without contamination but mostly in aseptic condition.

- Contaminated wounds: these are recent traumatic injuries with spillage from the infected site, non-purulent inflammation, with a high risk of septic condition.

- Dirty wounds: here the wounds contain purulent inflammatory tissues, foreign bodies, faecal matter or perforated viscera.

2.10.2 Surgical prophylaxis

Surgical prophylaxis is a process of administering an antibiotic to a patient before a surgical procedure, with the aim of avoiding a bacterial infection following an anticipated bacterial exposure (Wasserman *et al.*, 2014). Appropriate surgical prophylaxis is an effective way of addressing SSIs (Wanyoro *et al.,* 2013). Usually, a single dose is sufficient unless a repeat dose is required in cases where there are long surgical procedures or a large volume of blood is lost (Wasserman *et al.,* 2014). The SAASP, and Standard Treatment Guidelines and Essential Medicines lists for South Africa have recommended the use of cefazolin in most surgical procedures, however metronidazole is also given where anaerobic infection is anticipated. Other antibiotics such as ciprofloxacin, cefuroxime, vancomycin and chloramphenicol eye drops are recommended in certain specific surgical procedures (NDoH, 2015; Wasserman *et al.,* 2014). A review of RCTs, conducted by Cochrane in 2008 showed that short-term use of intranasal mupirocin ointment decreases the tendency of developing SSIs due to *S. aureus* with no chance of developing resistance (Van Rijen, 2009). Similarly, Wilcox *et al.* (2003) found that the use of prophylactic nasal mupirocin and 2% triclosan before orthopaedic operations resulted in a remarkable reduction of incidence of SSIs secondary to MRSA from 23/1000 surgeries to about 3.3 to 4.0/1000 surgeries, with a subsequent decrease in the demand for vancomycin by 23%.

Surgical prophylaxis is considered appropriate when the antibiotic is administered 0 to 60 minutes before first surgical incision or 120 minutes in cases where fluoroquinolones or vancomycin is used (Saied *et al.,* 2015). Antibiotic therapy should also not exceed a duration of 24 hours after surgical operation (Saied *et al.,* 2015). A study conducted in surgical settings of five Egyptian hospitals found that only a few hospitals had policies guiding general antibiotic usage or surgical prophylaxis. Additionally, no national guideline for

the optimisation of antibiotic therapy through AMS was available (Saied *et al.,* 2015). With the introduction of an educational intervention in these hospitals, a significant improvement was observed in the timing of the first dose of surgical prophylactic antibiotics in three hospitals with low support before the project from 0% - 6.7% to 11% - 38.7% in both pre-and post-implementation stages of the study, respectively (Saied *et al.,* 2015). There was also a reduction in the volume of antibiotic consumption in four hospitals from 843 Day of Therapy (DOT)/1000 patient days in the pre-intervention stage to 334 DOT/1000 patient days in the post-intervention stage. All the participating hospitals reported an improvement in the duration of surgical prophylaxis (Saied *et al.,* 2015).

Upon introduction of an educational intervention in thirteen Dutch hospitals, the volume of antibiotic consumption reduced from 121 DDDs/100 procedures in the pre-intervention stage to 79 DDDs/100 procedures in the post-intervention stage with a consequent reduction in antibiotic cost per procedure by 25% from € 10.96 to € 8.24 (Van Kasteren *et al.,* 2005). The number of cases with prolonged duration of inappropriate prophylaxis dropped to about 778 cases instead of 1,024 cases, the number of cases that received prophylaxis at an optimal duration increased from 805 (50%) cases pre-intervention to 1,197 (61%) post-intervention (Van Kasteren *et al.,* 2005). Cefazolin and metronidazole were the prophylactic drugs of choice if anaerobic bacteria were suspected during the study. Other agents used were first- and second-generation cephalosporins and co-amoxiclav in some surgical cases (Van Kasteren *et al.,* 2005).

2.11 ECONOMIC BURDEN OF ANTIBIOTIC RESISTANCE

Only a small number of studies on the economic implications of AMR in developing countries have been published. The WHO (2011a) reports that hospital acquired infections caused over 37,000 deaths with an additional 16 million days of admission in Europe at a cost of € 7 billion per annum. These figures are even higher in developing countries (Laxminarayan *et al.,* 2013). A report from the North-West province of South Africa showed that a full course of treatment of multidrug-resistant tuberculosis cost around R 26,354 (US$ 4,300) compared to R 215 (US$ 35) for drug-susceptible tuberculosis (Okeke *et al.,* 2005). Similarly, data from Peru has proven that the cost of treating

multidrug-resistant tuberculosis is far higher than drug-susceptible tuberculosis which was estimated at US$ 8,000 and US$ 267, respectively (Okeke *et al.,* 2005). Just over 50,000 lives are lost to antimicrobial resistance in Europe and the USA alone, leading to costs associated with loss of productivity (O'Neill, 2014).

As stated by the United States Centre for Disease Control and Prevention (CDC), about two million infections and over 23,000 mortalities occur annually because of antibiotic resistance in the United States (CDC, 2013). This amounts to a cost of US$ 20 billion with productivity losses of up to US$ 35 billion (CDC, 2013). Similarly, in Europe up to 25,000 deaths are linked to antibiotic resistance, with a financial loss of over € 1.5 billion (ECDC/EMEA, 2009). To assess the burden of AMR the United Kingdom government in 2014, under Prime Minister D. Cameron appointed Prof J O' Neil, an economist to chair a review of AMR (O'Neill, 2016). The work was carried out by two separate auditing firms to determine the future economic consequences of neglecting AMR; it was found that over 700,000 patients die every year because of AMR (Figure 2.4). It was forecast that if measures to contain antibiotic resistance are not taken, over 300 million people will die of infections from resistant organisms in the next 35 years (O'Neill, 2016). With the consequent reduction of up to 2% to 3.5% of the world's Gross Domestic Product, this means that US$ 60 to 100 trillion will be lost to AMR (Figure 2.5) (O'Neill, 2016). Based on this prediction 4,150,000 people from Africa will die every year (O'Neill, 2014).

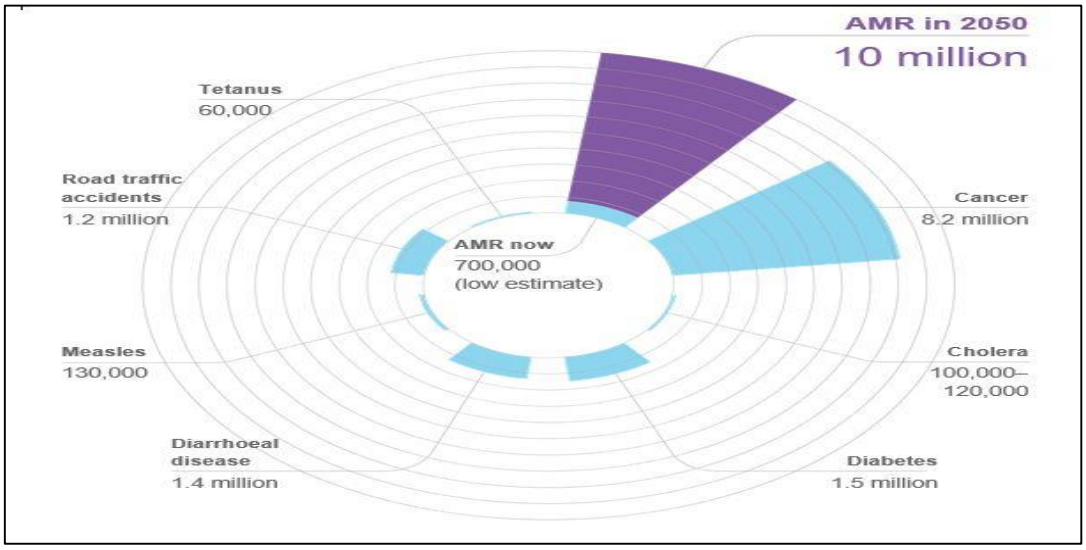

Figure 2.4: **Global** deaths due to AMR every year (O'Neill, 2016).

Even though reliable data on the economic implications of antibiotic resistance are lacking in developing countries, estimated attributable mortality rates have been calculated (Laxminarayan *et al.,* 2013). About 58,000 deaths from neonatal sepsis were found to be secondary to resistant bacterial infections in India alone (Laxminarayan *et al.,* 2013). Similarly, research from Tanzania and Mozambique shows an increased mortality in children under five years, because of difficult to treat bacterial infections (Kayange *et al.,* 2010; Roca *et al.,* 2008). Further research is required to determine the economic burden of these mortality rates.

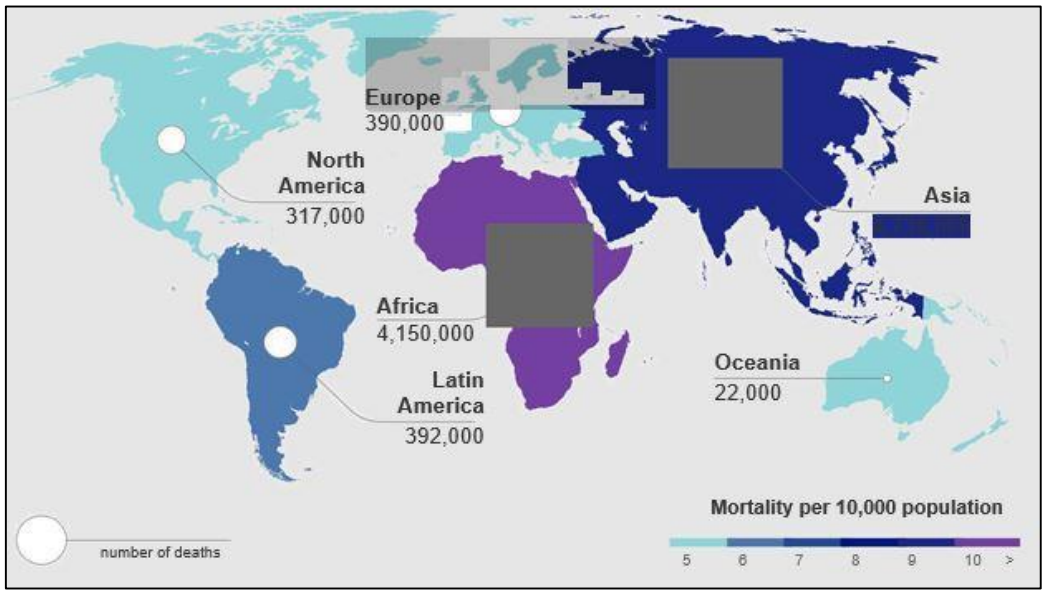

Figure 2.5: Predicted regional burden of AMR every year by 2050 (O'Neill, 2014).

2.12 OVERVIEW OF ANTIMICROBIAL STEWARDSHIP

The term "*Antimicrobial Stewardship*" was coined by two infectious diseases specialists McGowan JE and Gerding DN in 1996 (Mcgowan Jr and Gerding, 1996). However, programmes to optimise antimicrobial have been in existence since the 1970s, known as "*Antimicrobial management*" or *"Antimicrobial control"* projects (Bennett *et al.,* 2014). It is a multidisciplinary, systematic approach which reduces the duration of treatment, improves patient outcomes, minimises drug side effects, reduces drug costs, limits the emergence of resistance and ensures the safety of the patient (Fishman, 2012; Dellit *et al.,* 2007). According to Cruickshank (2011) AMS programmes, alongside infection

control, hand hygiene and surveillance are regarded as critical tools for preventing the emergence of AMR in our health facilities. The FDA is promoting AMS programmes in the United States by supporting the research and development of new antibiotics (Cunha *et al.,* 2013). In 2015, the WHO encouraged all member states to design a national plan on how to address the burden of AMR in two years (Figure 2.6) and it should include the following (WHO, 2015):

- Decrease demand for antimicrobial agents through the provision of potable water, sanitation and immunisation.
- Implement measures such as infection control and AMS policy at hospital level.
- Change attitudes that encourage antibiotic overuse and misuse to positions that support AMS.
- Encourage appropriate antibiotic use in agriculture.
- Enlighten the public, health care providers and policy makers on appropriate use of antibiotics and implications of antibiotics misuse.
- Political will to address the burden of antibiotic resistance.

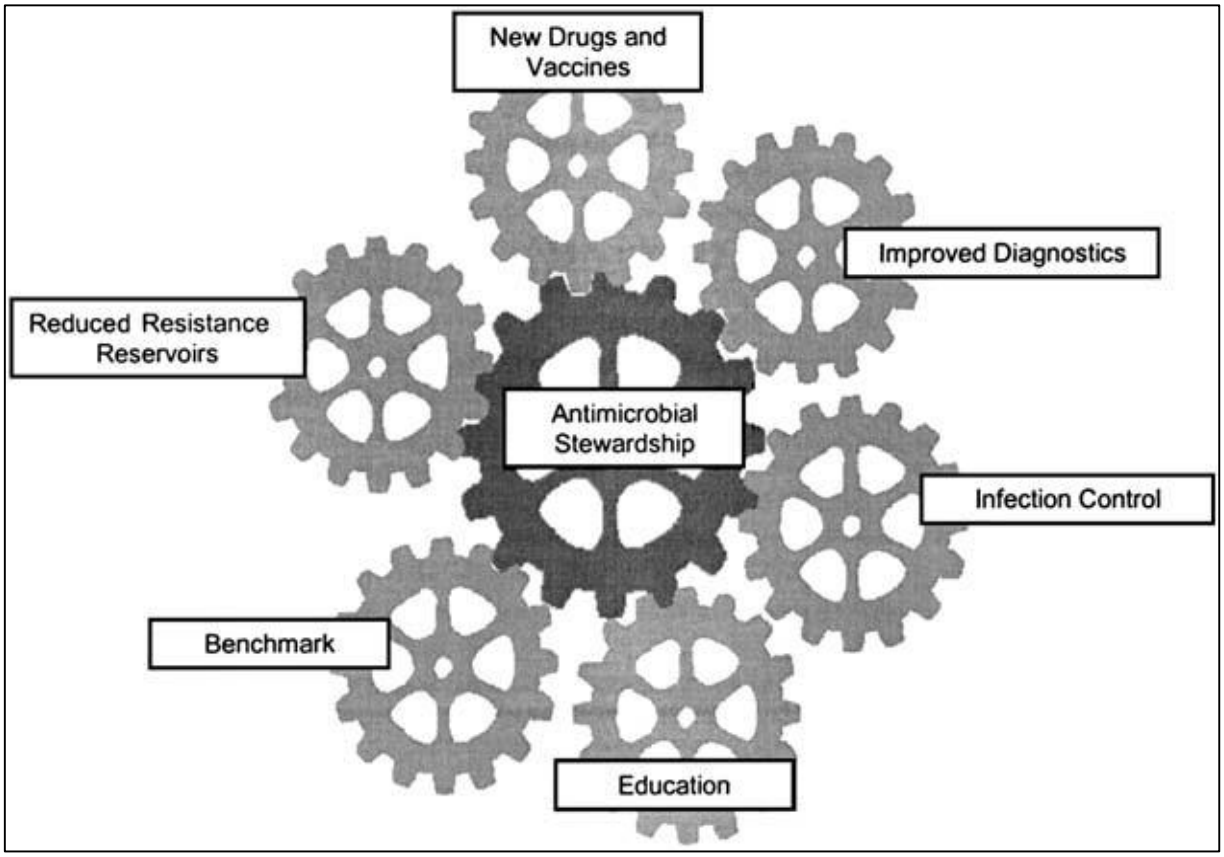

Figure 2.6: Strategies to contain antimicrobial resistance (Fishman, 2006).

The National Action Plan for Combating Antibiotic-Resistant Bacteria was launched by the United States government at the White House in March 2015, with it's goal to identify the need for all critical care centres in the United States to adopt AMS by 2020 in line with the CDC's recommendations (White House, 2015). Nursing homes, general outpatient departments, hospital wards and emergency units were also encouraged to adopt AMS programmes (Barlam *et al.,* 2016). Similarly, in South Africa, the GARP is collaborating with both public and private sectors to address this problem (Gelband *et al.,* 2015). In view of the constant danger caused by resistant pathogens and the uncertainty surrounding the development of new classes of antimicrobials, a need exists for the Health Service Executives in our hospitals to adopt AMS programmes (Roca *et al.,* 2015). In 2011, the AMS and resistance working groups of the International Society of Chemotherapy came up with recommendations to guide the appropriate use of antibiotics in hospital inpatients (Hara *et al.*, 2016). The IDSA in collaboration with the Society for Health Care Epidemiology of America has recently developed 27 recommendations to guide hospital AMS programmes (Barlam *et al.,* 2016). Global implementation of AMS is facing serious challenges especially in Low and Middle Income Countries, where it is mostly absent (Wertheim *et al.,* 2013b). Most hospitals in developing countries do not have AMS (Gelband *et al.,* 2015) with only 14% of hospitals in Africa having AMS compared with 46% and 53% in Latin American and Asian hospitals (Howard *et al.,* 2015).

Training and education in AMS is key. Incorporation of AMS and infection control courses into both undergraduate and postgraduate curricula of all health professionals will prepare them early enough to embrace the culture of appropriate prescription (Abbo *et al.,* 2013; Ashiru-Oredope and Hopkins, 2015; Thriemer *et al.,* 2013). Based on the findings of a survey conducted in thirteen European countries involving 35 medical schools, it was found that all the schools except one offered courses on AMS to undergraduate students but only one-third of these countries had implemented national programmes. (Pulcini *et al.,* 2015). Comprehensive AMS programmes have yielded a significant reduction in the use of antimicrobial agents, an increase in institutional cost saving, improvement in the appropriate use of antimicrobial agents, and a decrease in resistance rates, morbidity, mortality and hospital readmission

(Cruickshank, 2011; SARI, 2009). AMS provides a shorter duration of treatment and reduces hospital costs (Ohl and Ashley, 2011). In 2015, data on antibiotic consumption across European Primary Health Centres showed France as one of the countries with the highest rate of antibiotic consumption (ECDC, 2016). However, this is relatively stable in hospital environments, which is probably because the government has made it mandatory for hospitals in France to adopt AMS programmes before they can be given an operational licence (Le Coz *et al.*, 2016). Upon implementation of an AMS programme in acute care centres in 9 countries over a period of 14 years, there was a reduction in antibiotic consumption of 11% to 38%, as well as reduction in cost by US$ 5 to 10/patient/day (Kaki *et al.,* 2011). There was also an improvement in inappropriate antibiotic therapy and a reduction in average length of treatment (Kaki *et al.,* 2011). AMS also reduces hospital acquired infections (Davey *et al.,* 2017).

2.12.1 **Goals of antimicrobial stewardship**

- To partner with the physicians to ensure each patient receives optimal antibiotic therapy, by paying attention to the following “Ds” of appropriate antibiotic treatment: the “Ds” are right Drug, the right Dose, the best route of Delivery, attention to De-escalation and proper Duration of administration (Doron and Davidson, 2011; Joseph and Rodvold, 2008).
- To discourage unnecessary antibiotic usage especially in infections caused by viral agents (Doron and Davidson, 2011).
- To decrease chances of acquiring infections with difficult to treat bacteria such as *C. difficile* (Doron and Davidson, 2011).

2.12.2 **Antimicrobial stewardship in South Africa**

The Annual Conference of the Federation of Infectious Diseases of Southern Africa held on February 2012, gave birth to the South African Antibiotic Stewardship Programme with the following goals:

- To organise training on the appropriate use of antibiotics and share experiences with AMS to all South African health institutions and civil society groups.
- To establish strong leadership for strengthening AMS in both South African public and private health-care institutions.

- To develop a harmonised national guideline on antibiotic prescription out of the existing national guidelines, and include other infections, not in the guideline and incorporate improved diagnostic techniques.
- To recommend to the stakeholders the areas that need to be researched to bridge the gap of knowledge.
- To partner with the NDoH and other stakeholders in the private sectors (NDoH, 2014b).

In response to the WHO resolution *"Combating antimicrobial resistance including antibiotic resistance"* adopted by the World Health Assembly, the South African NDoH launched the Antimicrobial Resistance National Strategy Framework 2014 to 2024 (Figure 2.7) (NDoH, 2014b). These enablers were debated at a summit on AMR 2014 in Johannesburg and have since been accepted by the government of South Africa (Mendelson, 2015b).

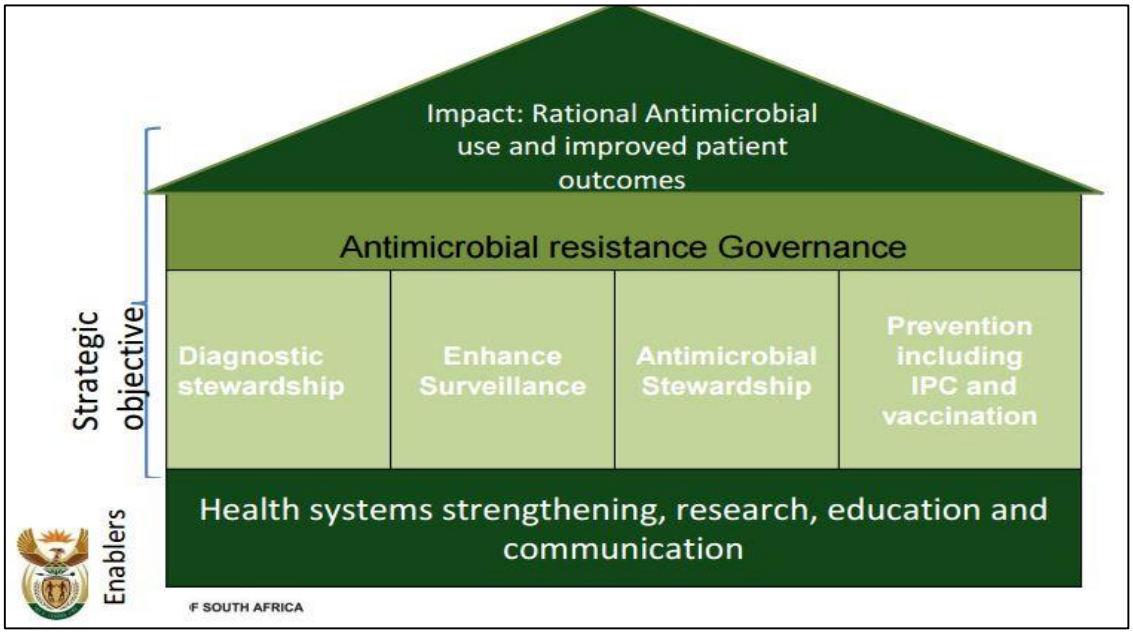

Figure 2.7: Pillars of South African AMR strategy framework (NDoH, 2014b).

The objectives are:

- Strengthen, coordinate and institutionalise interdisciplinary efforts.
- Enhance surveillance and early detection of antibiotic resistance.
- Optimise infection control and prevention.
- Promote AMS programmes.

While the four enablers being:

- Legislative measures to guide antimicrobial utilisation.
- Educational empowerment.
- Communication.
- Research (NDoH, 2014b).

2.12.3 **Antimicrobial stewardship strategies**

These strategies include;

2.12.3.1 **Education**

Education is an important strategy in AMS projects as it provides prescribers with new evidence and recommendations on how to prescribe antibiotics in line with best practices (Barlam *et al.,* 2016). Educational programmes like lectures and tutorials are more useful in academic and training hospitals than in non-academic hospitals (Barlam *et al.,* 2016). However, educational interventions alone without incorporation of other active strategies have been shown to play little role in changing prescribers attitudes and behaviour (Dellit *et al.,* 2007). Knox and Edye (2016) reported that implementation of education interventions alone in an Australian hospital did not show any significant difference in the compliance rate of surgical prophylaxis. The compliance rate before and after programme implementation was 18% and 15%, respectively.

2.12.3.2 **Formulary restriction and pre-authorisation**

This approach restricts access to certain antimicrobial agents, either because of their cost, adverse effects, or to delay the chance of bacteria developing resistance to these agents (Barlam *et al.,* 2016). Prior approval from the AMS team is required before the pharmacist releases specified restricted agents (Barlam *et al.,* 2016). This has been shown to reduce antimicrobial consumption, resistance and cost (Barlam *et al.,* 2016). Some of the limitations of this strategy are that it can often be bypassed and some physicians feel their autonomy to prescribe antibiotics is restricted (Gross *et al.,* 2001).

2.12.3.3 **Streamlining/de-escalation**

Streamlining is the process whereby a specialist reviews antibiotic treatment regimens and decides whether to discontinue, remove redundant combinations or narrow the therapy base on the results of the culture (Barlam *et al.,* 2016). A recent systematic review showed that guideline adherence and de-escalation are associated with 35% and 66% relative risk decreases in mortality (Schuts *et al.,* 2016). This reduces the number of antibiotics patients are receiving with a consequent reduction in cost. However, this strategy usually comes late after a patient has received certain inappropriate doses of antibiotics (Dellit *et al.*, 2007; Gross *et al.,* 2001).

2.12.3.4 **Conversion from intravenous to oral**

Converting a patients' antibiotic medications from intravenous to oral formulation is a major component of AMS programmes (Barlam *et al.,* 2016). It encourages an early switch as soon as the patient can tolerate oral formulations and there are no indications to continue with IV medications (Barlam *et al.,* 2016). This strategy also encourages the initial commencement of oral treatment in patients that can tolerate oral formulations especially regarding drugs with high bioavailability (Barlam *et al.,* 2016). This strategy lowers the cost, duration of hospital stay, the risk of developing sepsis and thrombophlebitis associated with a cannula (Barlam *et al.,* 2016).

2.12.3.5 **Antibiotic cycling**

Antibiotic cycling refers to periodic planned substitution of antibacterial agents that have been used for a while in a hospital or a unit with other drugs to lower the chances of pathogens selecting resistance to them (Dellit *et al.,* 2007). There is no substantive clinical evidence that antibiotic cycling has a beneficial effect in reducing resistance over a long period (Barlam *et al.,* 2016). However, use of an alternative agent may reduce the selective pressure and possible chances of resistance developing to the substituted agent (Dellit *et al.,* 2007).

2.12.3.6 **Institutional guidelines**

A well-designed guideline based on local resistance patterns reduces inappropriate empirical therapy. These guidelines need to be updated on a regular basis (Dellit *et al.,* 2007). Treatment guidelines for common clinical conditions are useful, especially for new professionals (Barlam *et al.,* 2016).

2.12.3.7 **Prospective audit and feedback**

This involves auditing of antibiotic therapy in line with laboratory results by the AMS team and sending feedback to doctors; this has been shown to increase appropriateness of antibiotic treatment (Brink *et al.,* 2016a).

2.12.3.8 **Dose optimisation**

This considers the individual patient characteristics, microorganisms causing the infection, pharmacokinetic and pharmacodynamic properties of the prescribed drug (Drew, 2009). It also involves adjusting the duration of therapy and dosing interval to ensure the required pharmacokinetic and pharmacodynamic properties are achieved (Drew, 2009).

2.12.3.9 **Antibiotic order form**

This plays an integral part in AMS and reduces the volume of antibiotic consumption by prescribing antibiotics with an automatic stop date. It may also encourage adherence to institutional guidelines (Drew, 2009; Dellit *et al.,* 2007).

Best Care Always (BCA), a South African private healthcare initiative, has adopted the following AMS interventions to reduce the effects of AMR: early conversion from IV to oral formulations; avoid use of antibiotics with overlapping activity unless there is clear indication; antibiotics should only be requested when they are absolutely needed and avoid unnecessary use of antibiotic therapy (Best Care Always, 2011). The guidelines also recommend sending appropriate specimens for culture and sensitivity routinely; laboratory results should guide antibiotic therapy; antibiotics should be prescribed at an appropriate dosage with correct frequency of administration and where empiric

antibiotic treatment is necessary, evidence-based guidelines should be adhered to (Best Care Always, 2011).

2.12.4 **Antimicrobial stewardship studies in South Africa**

There is limited study data on AMS in Africa (Brink *et al.*, 2016a). The first AMS study in Africa in a hospital setting was conducted in South Africa in 2013 (Boyles *et al.,* 2013). A study carried out at Groote Schuur Hospital, University of Cape Town, South Africa, showed that following the introduction of an AMS ward round and dedicated antibiotic charts in two wards; there was 19.6% and 35% reduction in total volume of antibiotics and pharmacy budget, respectively. No adverse effect was observed on inpatients or on 30 day-readmission following this intervention (Boyles *et al.,* 2013). In a private health care setting involving 47 Netcare hospitals in South Africa, a general pharmacist-led AMS programme which involved a prospective audit and feedback strategy resulted in a decrease in antibiotic consumption from 101.38 to 83.04 DDDs/100 patient days (Brink *et al.,* 2016a). A study at a trauma ICU of a tertiary health centre in Durban revealed that improved surveillance of bacterial pathogen along with an AMS programme encouraged appropriate empiric antibiotic usage with reduced demand for broad-spectrum antibiotics (Ramsamy *et al.*, 2013).

2.12.5 **Antimicrobial stewardship team**

The core members of this team are the infectious diseases specialists, clinical pharmacists, clinical microbiologists and hospital epidemiologists, even though they are not involved in the day-to-day activities of the team (Paskovaty *et al.,* 2005). Infection prevention and control nurses, where present, should be an integral part of the team (SARI, 2009). For the programme to succeed, hospital administrators must also be actively involved (Cruickshank, 2011; Goff *et al.*, 2017). The infectious diseases specialist usually serves as the team leader and is charged with the responsibility of determining appropriate use of antimicrobials, designing and modifying antimicrobial formularies, and educating colleagues on rational antibiotic use, and the review and implementation of guidelines (Paskovaty *et al.,* 2005). Clinical pharmacists, especially those with infectious diseases training assist with decisions regarding switching from intravenous to oral routes, prior approval and post-prescription assessment, drug purchases and dispensing (Paskovaty *et al.,* 2005). They also

offer expert advice on pharmacokinetics, practical and cost efficient use of antimicrobials, dose adjustments, approval of restricted antibiotics after consulting other team members, and advise on drug interactions and toxicity monitoring (Paskovaty *et al.,* 2005; SARI, 2009). A clinical microbiologist provides the team with data and information on resistance patterns (Dellit *et al.,* 2007). A hospital epidemiologist creates avenues to limit transmission of resistant pathogens, through examining the relationship between the nature of antibiotics use and trend of AMR (Paskovaty *et al.,* 2005).

An important factor obstructing the implementation of AMS in South Africa and other developing countries is the shortage of infectious diseases specialists to drive the process (Brink *et al.,* 2016b). The Netcare model in which a general pharmacist drove the project without specific infectious disease training is an assurance that AMS can successfully be implemented in a resource-limited setting of Africa (Brink *et al.,* 2016b). Charani and Holmes (2013) proposed that in a resource constrained setting, rural and district hospitals can collaborate with academic hospitals with established AMS programmes; they can also design simple interventions to address factors associated with inappropriate antibiotic consumption. Recently South Africa designated two centres to train pharmacists from regional hospitals across the regions on AMS to be able to implement these programmes in their various hospitals (Brink *et al.,* 2016b).

The role of nurses has not been clearly defined in most AMS guidelines, unlike pharmacists whose involvement ranges from dose optimisation to leading AMS programmes (Olans *et al.,* 2016; Schellack *et al.,* 2016). However, nurses may play a critical role in AMS especially in a resource constrained setting like Africa. As health professionals in close contact with patients, nurses can help in ensuring patients receive their antibiotics as prescribed, report adverse events, allergies and side effects (Edwards *et al.,* 2011). A study conducted across 33 private sector hospitals in South Africa showed how nurses and pharmacists played a significant role in reducing antibiotic ‘hang time’ (Messina *et al.,* 2015).

2.12.6 **Antimicrobial stewardship in surgical settings**

Surgical wards are often a setting for high levels of antibiotic consumption and therefore the opportunity for inappropriate antibiotic utilisation and the

development of antibiotic resistance is substantial. There are limited studies on AMS in surgical settings. In 2002, one of the first AMS programmes in a surgical setting was launched at the surgical ICU of the University of Szeged Hungary, where critically ill orthopaedics, neurosurgical and trauma cases were managed (Peto *et al.,* 2008). A policy to restrict the use of certain antibiotics was implemented with an infectious diseases specialist and a microbiologist conducting an AMS ward round 5 times a week (Peto *et al.,* 2008). A substantial reduction in consumption of antibiotics was recorded from 162.9 DDDs/100 patient days' pre-intervention to 101.2 DDDs/100 patient days' post-intervention (Peto *et al.,* 2008). The reduction was linked to the decline in the use of quinolones, aminoglycosides, metronidazole and carbapenems (Peto *et al.,* 2008). The consumption of 3rd generation cephalosporins was reduced by nearly 50%, from 11 to 6.1 DDDs/ 100 patient days. However, the utilisation of 2nd generation cephalosporin rose to 39.1 from 29.5 DDDs/ 100 patient days (Peto *et al.,* 2008). In Canada, an AMS intervention programme involving the use of a local guideline, education programmes, pocket cards, posters, and regular academic meetings was implemented at the Surgery Department of tertiary public teaching hospital (Popovski *et al.*, 2014). This led to decreased consumption of ciprofloxacin from 221 to 74 DOT/1000 patient days, and piperacillin/tazobactam from 116 to 67 DOT/1000 patient days, with an increase in the utilisation of ceftriaxone from 6 to 92 DOT/1000 patient days (Popovski *et al.*, 2014).

At the neurological ICU of the Freiburg University Hospital Germany, a guideline for the treatment of hospital- and community-acquired pneumonia in patients with neurosurgical problems was amended in 2004 (Meyer *et al.,* 2007). The duration of therapy for hospital-acquired pneumonia was shortened from 14 to 7 days; while that of community-acquired pneumonia decreased from 10 to 5 days with patients being regularly reviewed by an infectious diseases physician, a microbiologist and a pharmacist (Meyer *et al.,* 2007). The volume of antibiotic consumption was reduced to 626.7 from 949.8 DDDs/1000 patient days because of the intervention. The reduction in antibiotic density was attributed to decreased use of 2nd generation cephalosporins, imidazole, β-lactams and glycopeptides. The antibiotic cost per patient day reduced from € 13.16 down to € 7.31 following the intervention (Meyer *et al.,* 2007). An AMS at an orthopaedic

surgery unit in Germany which involved a weekly antibiotic round, telemedicine consultation, bedside teaching and review of local guideline, resulted in significant reduction in antibiotic usage between the two study stages from 334.9 to 221.4 Recommended Daily Doses, with an overall monthly cost saving of € 2,575 (Borde *et al.*, 2016).

2.12.7 **Impact of AMS on cost and resistance**

In a study conducted in Michigan USA to assess the cost-effectiveness of an AMS programme, usage of eight antibiotics was assessed: daptomycin, ertapenem, aztreonam, voriconazole, meropenem, caspofungin, tigecycline, and linezolid (Malani *et al.,* 2013). A 15% reduction in the budget was observed from US$ 1,503,748 to US$ 1,274,837, resulting in savings of US$ 228,911 a year after instituting the policy (Malani *et al.,* 2013). Also, a significant decrease in the budget of the target antibiotics was observed from US$ 462,404 down to US$ 297,851, equivalent to 35.6% with a saving of US$ 164,553. A 25.4% reduction in consumption of the target antibiotics was seen from 215.7 DDDs/1000 to 160.8 DDDs/1000 patient days (Malani *et al.,* 2013). Dellit *et al.* (2007) reported a 19% reduction in antibiotic expenditure with a consequent increase in hospital saving of US$ 177,000 after the introduction of an educational intervention in the form of written or verbal instructions to prescribers.

Bantar *et al.* (2003) in Argentina employed four steps, namely baseline data collection, the introduction of a prescription form, education and prescription control, to implement AMS. The AMS team could modify dosing, narrow the antibiotic regimen and shorten the duration of treatment. A persistent reduction in antimicrobial consumption was observed with a total cost saving of US$ 913,236. There was also a reduction in resistance of *Proteus mirabilis* and *Enterobacter cloacae* to ceftriaxone (Bantar *et al.,* 2003). Similarly, Saizy-Callaert and colleagues conducted a study in which four multidisciplinary measures were employed (1) develop a prescription form through consensus with all prescribers (2) restricting prescriptions of most expensive antibiotics (3) regular assessment and audits of prescribed antibiotics (4) training of prescribers (Saizy-Callaert *et al.,* 2003). Drugs were only released if validated by a pharmacist. It was reported that a significant reduction in the rate of

unjustified prescriptions and the antimicrobial cost per inpatient day also fell drastically from US$ 13.8 million in 1997 to US$ 11 million in 2000. Although the prevalence of MRSA and CRE remained stable, a significant reduction in *Enterobacteriaceae* producing extended-spectrum β-lactamase was observed (Saizy-Callaert *et al.,* 2003).

According to Feucht and Rice (2003) concerns were raised about an increase in the unnecessary use of parenteral vancomycin and fluoroquinolones in the treatment of Gram-negative bacteria at a Veterans Affairs Medical Centre in the USA. A computerised review of patients on intravenous vancomycin and fluoroquinolone for more than 48 hours was initiated. If the team decided the choice of antimicrobial was inappropriate, the prescribing doctor was contacted. Following this, a change was made to the prescription. Using this intervention an overall reduction of cost of nearly US$ 48,000 from 1998 to 2011 was observed. During this stage, a 43% decrease in the use of intravenous fluoroquinolone was noted along with a 16% reduction in inappropriately prescribed vancomycin (Feucht and Rice, 2003). The impact of using a computer-assisted screening programme in the United States to eliminate redundant antibiotic combinations in a pharmacist-based intervention in a public teaching hospital was assessed (Glowacki *et al.,* 2003). Almost 192 patients 16.1% out of 1,189 patients were found to be receiving redundant antibiotic combinations, and this was commonly seen in ICU and surgical units compared to medical units. Interventions recorded a 98% success rate with a saving of US$ 10,800 and a reduction of 584 days from a redundant antibiotic combination (Glowacki *et al.,* 2003). The focus of AMS programmes is to improve appropriate antibiotic utilisation, but hospital management is also motivated by the cost implications of implementing such projects (Beardsley *et al.*, 2012). An academic hospital in Taiwan spent a sum of US$ 3,935 every month as a cost of implementing AMS programmes by an infectious diseases physician, two clinical pharmacists and two infection control nurses (Lin *et al.*, 2013). In three years, the programme saved the hospital a sum of US$ 2,495,954 and they paid a total of US$ 141,660 to the AMS team for implementing the programme (Lin *et al.*, 2013).

2.12.8 **Antimicrobial stewardship care-bundles**

Bundles are collections of 3 to 5 simple evidence-based practices that when employed simultaneously will enhance the patient's clinical condition (Resar *et al.,* 2012). These tend to have a better impact than applying individual practices independently (Resar *et al.,* 2012). Antibiotic care bundles are the easiest way of implementing AMS policies to patients (Cooke and Holmes, 2007). The idea of using bundles in the treatment of patients was first brought about in 2001 by the Institute for Health Care Improvement, with bundles providing an opportunity for all patients to receive regular and optimal care always (Resar *et al.,* 2012). Antibiotic care bundles decrease the chances of resistance and transmission of *C. difficile* (Cooke and Holmes, 2007). It also reduces the likelihood of contracting hospital-acquired infections by reducing the duration of hospital stay. It should be noted that the absence of one of the components of bundle should not delay commencement of antibiotics in emergency situations (Cooke and Holmes, 2007). In South Africa, the BCA has developed an AMS bundle to guide the use of antibiotics for both treatment and prophylactic purposes (Best Care Always, 2011). Upon admission, a member of the AMS team should determine the probable cause of infection; whether an appropriate clinical specimen has been sent for analysis; whether an infection is community or hospital acquired and on day seven decide on whether to continue or stop therapy. For prophylactic usage, the AMS team should also determine; whether a prophylaxis is required in a procedure and agent was appropriately chosen; whether given 0 – 60 minutes before surgical incision and stopped within 24 hours (Best Care Always, 2011).

2.12.9 **Role of biomarkers in antimicrobial stewardship**

Moribund patients with sepsis are usually on prolonged courses of antibiotics that encourage resistance. Procalcitonin (PCT) is a precursor in the synthesis of calcitonin and is used to guide and monitor antibacterial therapy more reliably than white cell count and C - reactive protein (CRP) (Nobre *et al.,* 2008). The CRP biomarker, though not as accurate as PCT (Zhang and Singh, 2015) in guiding antibiotic therapy, can be used to reduce inappropriate antimicrobial therapy. CRP takes 36 to 50 hours to reach it's peak level after bacterial infections (Sullivan and Von Rueden, 2016), while PCT values rise within two hours in response to bacterial stimuli and reaches it's peak level at 24 hours

(Foushee *et al.*, 2012). A RCT conducted across Vietnamese Primary Health Centres, among patients managed for simple acute respiratory tract infections, show a reduced antibacterial consumption among group of patients in which CRP was requested (n = 581/902; 64.4%), compared to the control group (n = 738/947; 78%) in which CRP was not requested (Do *et al.*, 2016). A similar trial in developed countries showed a reduced demand for antibiotics among the CRP - requested groups (n = 631/1685; 37.5%) compared to the control group (n = 785/1599; 49.1%) (Aabenhus *et al.*, 2014). Table 2.2 shows the NHLS guideline for use of biomarkers in South Africa (NHLS, 2012). Surgeons should bear in mind that surgical operations, trauma, renal replacement therapy, multiple organ failure and burns are factors that elevate PCT values without infections (Hohn *et al.*, 2017). PCT has been shown to encourage rational antibiotic utilisation, reduces chances of developing AMR and decreases the cost of antibiotic therapy (Sullivan and Von Rueden, 2016).

Table 2.1: National Health Laboratory Services Guideline for the use of biomarkers (NHLS, 2012).

Biomarkers	**Clinical condition**	**Reference range**
Procalcitonin (µg/L)	Lower Respiratory Tract Infection	<0.1 – No signs of any bacterial infection
		0.1 - 0.25 – Localised bacterial infection unlikely
		0.25 - 0.5 – Localised bacterial infection possible
		>0.5 – Suggestive of bacterial infection
	Systemic bacterial infection/sepsis	<0.5 – Systemic infection unlikely but localised infection not excluded
		0.5 - 2 – Systemic infection possible
		2 - 10 – Suggestive of systemic infection
		>10 – Severe systemic infection/septic shock
C - Reactive Protein (mg/L)		<10
White Cell Count		3.90 - 12.60

A RCT showed that PCT could be used to guide antibacterial therapy with serial PCT assays being utilised as a guide to reducing days of antibiotic treatment (Bouadma *et al.,* 2010; Hochreiter *et al.,* 2009; Nobre *et al.,* 2008; Schroeder *et al.,* 2009). The use of this marker to monitor therapy among severely ill patients

in ICU battling with sepsis has led to the reduction of 2 to 4 antibacterial-free days without any significant difference in 28 days' mortality (Prkno *et al.,* 2013). Clinical evidence advises against a delay in commencement of antibiotics in severely ill patients with negative PCT (Jensen *et al.,* 2011; Layios *et al.,* 2012). A 2015, study conducted in a Chinese hospital to assess the impact of implementing PCT-guided antimicrobial therapy in patients with acute respiratory infections, noted a considerable reduction in the cost of treatment (Stojanovic *et al.*, 2016). The intervention resulted in a 38.9% reduction of antimicrobial cost from ¥ 1.8 million (US$ 288,000) among the cohort of patients in which PCT was not used to ¥ 1.1 million (US$ 176,000) in a group in which PCT was used to guide the therapy. The hospital saved a sum of ¥ 250,699 (US$ 40,112) and ¥ 2.4 million (US$ 384,000) in the ICU and outpatient department, respectively (Stojanovic *et al.*, 2016). In contrast, the introduction of an AMS programme along with PCT-guided antimicrobial therapy at a surgical ICU of a German hospital resulted in a 21% reduction of antimicrobial usage from 1,005 DDDs/1000 patient days in 2010 to 791.9 DDDs/1000 patient days in 2012 (Hohn *et al.*, 2015). This has led to a decreased utilisation of aminoglycosides, quinolones and cephalosporin with a relative increase in the consumption of carbapenems. The interventions also decreased the cost of antibiotics from € 54,498 to € 33,297 over 3 years (Hohn *et al.*, 2015).

The following guidelines were adopted by a surgical ICU to guide the use of PCT among patients on antimicrobial therapy in Germany (Hohn *et al.*, 2015; Hohn *et al.*, 2017). Commencement of antibiotics is based on clinical evaluation; daily monitoring of PCT in patients on antibacterial agents for the first 3 days of admission or from when the diagnoses of suspected systemic bacteria is made; from the fourth day of antibiotic therapy, PCT is assessed every other day and consider stopping antimicrobial therapy when the PCT level is ≤ 0.25 ng/ml, with signs of clinical improvement; it is also recommended to discontinue antibiotic therapy when the PCT level is between >0.25 and <0.50 ng/ml or reduces to 10% from its highest level (Schuetz *et al.*, 2015). The use of PCT to guide antibiotic therapy in patients with acute respiratory tract infection attending hospitals in the United States has shown a significant reduction of antibiotic cost. A sum of US$ 6,409,179 was saved from a US$ 12,296,714 spent on antibiotic therapy in a group of patients in which PCT was not used to guide

therapy, compared to US$ 5,887,535 in a group in which PCT was used to guide treatment (Schuetz *et al.*, 2015).

2.12.10 **Barriers and limitations to successful AMS**

Although AMS has the potential benefit of improving appropriate antibiotic utilisation, improving clinical outcomes, reducing antibiotic resistance and cost, there are barriers to the successful implementation of AMS which include lack of staff commitment, lack of funding and collaboration between healthcare professionals. Limitations in education and funding have also contributed to poor implementation of AMS programmes.

2.13 **DRUG UTILISATION REVIEW**

According to the WHO drug utilisation review (DUR), also known as drug use evaluation *"refers to a system of continuous, systematic, criteria-based drug evaluation that ensures the appropriate use of the drug"* (WHO, 2003). It also involves ways of capturing data on problems relating to drug consumption, developing strategies for solving these problems, thereby improving appropriate drug treatment (WHO, 2003). In drug utilisation review studies, electronic medical records and records from pharmacy databases provide superior and more reliable information than records from patient files, wholesale data or information from patients during interviews (Schneeweiss and Avorn, 2005). Regular assessment of the pattern of antibiotic consumption in hospitals with feedback to the prescribers and decision makers can go a long way in encouraging prescribers to embrace the culture of rational antibiotic prescription (Hutchinson *et al.,* 2004).

To date, there is no single standard unit of measurement of drug consumption across all clinical settings globally. However, the DDD has been recognised by the WHO (Ashiru-Oredope and Hopkins, 2015). Norwegian researchers working in collaboration with the Nordic Council on Medicine came up with the concept of DDDs as a way of quantifying drug use in 1976 (Monnet, 2007). Similarly, Norwegian researchers also developed the Anatomical Therapeutic Chemical (ATC) drug classification in the 1970s (Hutchinson *et al.*, 2004) by reviewing the classification of the European Pharmaceutical Market Research Association (WHO, 2003). It classifies medicines into different categories based on targeted

organ-systems and their chemical or curative properties. Every drug has a minimum of one ATC code which is further subdivided into five various levels (Hutchinson *et al.,* 2004). For instance, all amoxicillin/clavulanic acid preparations are given J01CR02 as their ATC code (Appendix 1), an agent may have several ATC codes due to its different therapeutic uses such as prednisolone, however, this is not common with antibiotics (WHO, 2016a).

The WHO European office approved the use of ATC/DDD methodology for drug utilisation review in 1981 (Monnet, 2007). Following this in 1982 the WHO Collaboration Centre for Drug Statistics Methodology was launched which receives applications for assignment of ATC codes and DDDs for new drugs (Monnet, 2007). In 1996, the WHO International Working Group for Drug Statistic Methodology was launched and it receives applications and assumes the responsibility of assigning ATC codes and DDDs after a comprehensive literature consultation (Monnet, 2007; Sketris *et al.,* 2004).

2.13.1 **Anatomic Therapeutic Chemical (ATC) classification**

The ATC classification system places active ingredients of drugs into different groups based on the body organ system upon which they exert their therapeutic, pharmacological and chemical actions (WHO, 2016a). Drugs are categorised into groups and further subdivided into five different levels (WHO, 2016a). There are 14 main categories (first level), then pharmacological/therapeutic subgroups (second level), the third and fourth levels are chemical/pharmacological/therapeutic subgroups, while the fifth level is the chemical substance (WHO, 2016a).

2.13.2 **Defined Daily Doses**

The WHO has defined DDD in human medicine as "*the average maintenance dose of the drug when used for its primary indication in adults"* (WHO, 2003). For instance, paracetamol has a DDD of 3 grams as assigned by WHO, so an average patient (70kg) who received paracetamol for its primary indication of pain relief, would have consumed 3g per day. This is equivalent to 6 tablets of 500mg of paracetamol daily. If a patient consumes 24 of these tablets (12g of paracetamol) over a specified period, this equal to the consumption of 4 DDDs

$$Drug\ usage = \frac{24\ X\ 500mg}{3g} = 4$$

The DDD metric has existed for many years and has been widely reported in many studies (Chauvin *et al.*, 2001). It allows tracking of the volume of antibiotics consumed by an organisation over a period both regionally or nationally by considering the regional or national population as a denominator. It also allows for international comparisons between different studies (Ashiru-Oredope and Hopkins, 2015). The process of comparing antibiotic utilisation between hospitals, regions or countries is called *benchmarking* (Polk *et al.,* 2007; Shetka *et al.,* 2005).

Only drugs with assigned ATC codes can be given a DDD (WHO, 2016a). Every medicine is given a DDD at its 5th level of ATC classification. A medication may have more than one WHO assigned DDD depending on the formulation (Hutchinson *et al*., 2004). For example, the intravenous formulation of amoxicillin/clavulanic acid = 3 DDDs, while the oral formulation = 1 DDD (WHO, 2016a). The DDD for a drug is usually given after it has been released on the market and reviewed for three years after monitoring its use and recommendations from different countries (Chauvin *et al.,* 2001). Drug utilisation is often expressed as DDDs/1000 patients' days or alternatively DDDs/100 bed-days when reporting consumption of inpatients, but for medicines used for short durations it's preferable to report the values in DDDs/inhabitant/year (Kuster *et al.,* 2008; WHO, 2003). The IDSA has adopted the use of DDDs/1000 patient days for measuring antibiotic utilisation in AMS studies (Dellit *et al.*, 2007). However, recently DOT is gaining popularity in the United States (Barlam *et al.,* 2016). The DDDs enable easy comparison between hospitals, and can also be used to quantify the volume of antibiotic consumption in a setting that has no established computerised pharmacy records, such as in developing countries (Polk *et al.,* 2007). It is worth noting that the DDD does not necessarily correspond to Prescribed Daily Dose (PDD) because drugs are prescribed to patients based on their age, weight and pharmacokinetic factors (WHO, 2003). Also, some prescribed medications are not dispensed, and patients do not always take all their medications that are dispensed (WHO, 2003).

2.13.3 Limitations of using DDD techniques

Limitations in using DDDs are generally related to altered dosing such as use in renal or hepatic impairment or paediatrics. The DDD usually gives a lower value in patients who had their antibiotics adjusted because of compromised renal function (Shetka *et al.*, 2005) compared to individuals with normal renal function (Zagorski *et al.,* 2002). The DDD methods will underestimate antibiotic exposure when the administered daily dose is reduced for a patient with renal failure (Polk *et al.,* 2007). This is relevant in benchmarking between hospitals, where the proportion of patients with renal failure in one hospital is different from that of another hospital (Polk *et al.,* 2007). In a study to evaluate the effect of renal insufficiency on DDD in a group of patients receiving ceftriaxone, levofloxacin or vancomycin, two methods of quantifying antimicrobial duration of therapy (Stop-Start Days and Transaction Days) were used (Zagorski *et al.,* 2002). The vancomycin use rate for patients with renal insufficiency was 36% lower than that of patient with normal function for DDDs; and this was 23% lower for Transaction days; for levofloxacin, there was a 27% rate reduction for DDDs. No significant reduction was observed when the Stop-Start Day method was used. Compared with the DDD method, measures of therapy duration are less affected by renal function and may improve comparison between populations (Zagorski *et al.,* 2002). The DDD method is also not applicable in a paediatric population (Shetka *et al.,* 2005). Drugs such as topical preparations especially dermatological agents, along with cytotoxic medications, anaesthetic agents and vaccines have no assigned DDD (WHO, 2016a). Topical preparations are not usually given a DDD because the dose administered per day depends mainly on the extent and severity of the clinical condition (Sketris *et al.,* 2004).

2.13.4 Prescribed Daily Dose

PDD is an average daily prescribed dose of a certain number of prescriptions and it is usually obtained by review of patient's prescriptions or pharmacy records (WHO, 2003). For drugs with different dosage regimens depending on the clinical condition it is being used for, it is important to take diagnoses into consideration when calculating PDD; because a drug with various indications tends to have a different PDD depending on the condition (WHO, 2003). This unit of measurement is commonly employed in studies aimed at determining the pattern of prescription (Chauvin *et al.,* 2001). It is also useful in determining

doctor's prescription habits and prevalence of morbidity (Merlo *et al.,* 1996). The PDDs tend to differ from one country to another, and it is also affected by the severity of the clinical condition being managed. All these should be taken into consideration when using PDD to make a comparison between countries (WHO, 2003). The PDD does not always give an accurate picture of drug utilisation because not all patients complete their dosages especially in outpatient settings. Therefore, to measure actual drug use by the patients, the patients need to be interviewed to know the level of drug intake the so-called consumed daily doses (WHO, 2003).

2.13.5 **Days of Therapy**

A single day of therapy (DOT) of a drug refers to a single drug agent delivered to a patient per day irrespective of its strength or frequency of delivery (Polk *et al.,* 2007). The use of the DOT metric to determine the volume of antibiotic utilisation in the USA is gradually replacing DDD (Ibrahim and Polk, 2014). A digital pharmacy record is required to accurately measure it, which is absent in most developing countries and it is therefore difficult to use this metric to make an international comparison and therefore the DDD is still most widely used in developing countries (Monnet, 2007).

2.13.6 **Minimum Marketed Dose**

The Minimum Marketed Dose is the minimum dose needed to produce a required therapeutic effect and its equivalent to the minimum dose marketed by the producer (Chauvin *et al.,* 2001). A similarity exists between Minimum Marketed Dose and DDDs as both define the amount of drug, but DDDs give additional information on daily quantity, which is independent of the number of doses per day (Merlo *et al.,* 1996).

2.13.7 **Equipotential Dose**

Two Danish doctors developed the Equipotential Dose with a focus in the treatment of hypertension; it refers to the active substance in each drug having the same effect on blood pressure (Merlo *et al.,* 1996).

2.13.8 **Cost**

Though price can be used to determine total drugs expenditure, it plays little role in evaluating drug utilisation. It is difficult to make a comparison between countries using this metric measure, because it is easily affected by inflation, national regulatory policies, price fluctuations and exchange rate variations (WHO, 2016a).

2.13.9 **Other methods of quantifying drug utilisation**

Some of the less commonly used methods of estimating drug consumption include the number of packages, the number of prescriptions, number of tablets and gram of active ingredients. These are useful when evaluating a single agent, but none of these can be used to compare the volume of consumption between countries (WHO, 2003; Shetka *et al.,* 2005).

CHAPTER THREE: RESEARCH DESIGN AND METHODS

3.1 INTRODUCTION

This is a quantitative study combining a prevalence cross-sectional and observational, descriptive study with an intervention study. The study was divided into two stages; in the first stage the data was collected retrospectively, and in the second stage it was prospectively collected.

3.2 RESEARCH DESIGN

3.2.1 Setting

The study was conducted at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), Gauteng Province, South Africa. The CMJAH is a 1,088-bed tertiary academic hospital located in Johannesburg, Gauteng Province. It provides a full range of care including general, vascular, orthopaedics, neurosurgery, organ transplant and gastrointestinal surgeries, it also has many diagnostic facilities. It serves as a training and research facility for students of the University of the Witwatersrand and it is also a referral centre for many other hospitals in Gauteng province. The two surgical wards selected for this study were the Vascular and General Surgery Wards. The Vascular Ward has 24 beds with four extra beds in side rooms for isolation and critical cases. It is headed by a Professor of Vascular Surgery with consultants, fellows, registrars and interns under his supervision. A wide range of cases are admitted and managed in this ward which include; chronic and acute vascular ischemic diseases, diabetic foot diseases, stab injuries and many other vascular conditions. Sometimes other surgical conditions are transferred from other surgical units when there are bed space shortages. Surgical procedures performed on patients in this unit include vascular bypass surgeries, amputations, vascular injury repairs, angiograms, angioplasties, as well as a variety of other procedures. Many of the patients in this ward are mostly middle aged or elderly with one or more chronic conditions and multiple co-morbidities.

The General Ward is also under the supervision of a Professor of Surgery with consultants, fellows, registrars and interns working under him. They treat cases such as hepatobiliary and abdominal malignancies, appendicitis, pancreatitis,

various forms of upper and lower gastrointestinal conditions and a full range of general surgical conditions. The ward has 24 beds with five extra in side rooms for isolation and critical patients and patients of all ages from 18 years are treated here. A full range of surgical procedures for acute and chronic surgical conditions are performed, and these include cholecystectomies, appendicectomies, abscess drainage, herniorrhaphies, colostomies, pancreatectomies, splenectomies amongst others. The two wards were selected for the study because of high antibiotic consumption and high turnover of patients.

3.2.2 **Study design**

The study was conducted in two stages.

3.2.2.1 **Stage 1: Cross-sectional observational and descriptive study**

In this stage, patient record data was collected retrospectively in two of the study wards and served as the control stage as well as a situational review (Appendix 2). Records of 264 patients who were given antibiotics during their inpatient stay and met study inclusion criteria were reviewed from February to May 2016 (Appendix 3). The parameters evaluated in this study include antibiotic use, indication for antibiotic therapy, dosage and route of administration, appropriate duration of treatment and de-escalation to a narrow-spectrum in line with microbiological investigation results. The costs of antibiotic treatment and pathology tests were determined. The volume of antibiotics consumed was measured using DDDs/1000 patient days. The appropriateness or otherwise of antibiotic prescriptions was determined using a guideline developed by Gyssens and colleagues in 1992 (Appendix 4) (Plenat *et al.,* 1992). The appropriateness of surgical prophylaxis was determined based on the recommendations of SAASP (Wasserman *et al.,* 2014) and Standard Treatment Guidelines and Essential Medicines Lists for South Africa (NDoH, 2015). The appropriateness of other forms of prophylaxis in which fluconazole was used in patients with suspected intra-abdominal sepsis was determined. Regarding the choice of prophylactic agent, dose, and duration, the incision time was not assessed because such record was not found in most of the patient's files (NDoH, 2015). Patient diagnoses were categorised and type of surgical procedure was determined based on the type of wound.

3.2.2.2 **Stage 2: Intervention study**

The intervention involved a dedicated AMS weekly round in each of the two surgical wards; which was separate to the general daily ward rounds. Ward rounds were started on the 20th May 2016. Two weeks were allowed for the doctors, nurses, and other professionals in the wards to become familiar with the study. Intervention data were not collected during this stage. Data collection began on 3rd June 2016. Ward rounds consisted of making recommendations on the patient files based on AMS guidelines. Fellows, resident doctors, and the interns participated in the rounds and assisted by explaining the rationale behind the choice of antibiotics. The infectious diseases consultant discussed each condition at the bedside, especially regarding antibiotics selection, laboratory investigations and emphasis on collecting appropriate specimen and culture directed therapy. The intervention also involved dose optimisation and adjustments of dose in patient with renal and hepatic impairment. This stage lasted for four months from June to September 2016, and a total of 212 patients who met the inclusion criteria and agreed to participate in the study were included.

The AMS ward round was led by an infectious diseases specialist. Microbiologists were not able to participate in the weekly round due to a conflict with other functions on the same day. A pre-round was conducted on Thursday by the investigator to identify patients on antibiotics that met the inclusion criteria, obtain their consent to review their records and their permission to participate in the study. Patient demographics, antibiotic utilisation information and available results of the investigation in the patient files were reviewed during the pre-round. Laboratory results not available in the patient files were retrieved from the microbiology computers in the record room to assist in deciding whether the treatment was appropriate or otherwise, to de-escalate or stop the treatment. Appropriateness of antibiotic utilisation, antibiotic cost and volume of drug consumption were determined as in the first stage. Each ward round began at 8:30 am every Friday, usually starting in the Vascular Ward before proceeding to General Surgery Ward. Each round took an average of two hours. During the AMS round, all patients on antibiotic treatment were evaluated, but the data was collected only on those with signed consent. Each case was discussed to determine the appropriateness and rational of antibiotic choice or otherwise of

therapy. During rounds the following recommendations could be made based on the patient clinical condition; early conversion from intravenous to oral formulations, change in duration or frequency of treatment, conversion from broad-spectrum to a narrow-spectrum antibiotic base on the culture result, discontinuation of antibiotic therapy when there is no indication or when antibiotics with overlapping activities are used, encourage early removal of drains, cannulae and catheters when their functions are not required. Others included dosage adjustment of dose in patients with renal or liver dysfunction. Recommendations were also made on the collection of appropriate specimens for culture. Where required, discussions were held with the Head of Infectious Diseases unit as well as senior doctors in surgery on the rational antibiotic usage and implication of unnecessary antibiotic prescription in specific patients. All patients that were seen during the antibiotic round were followed up until discharge to assess the implementation of the recommendations and capture their data.

3.3 RESEARCH METHODS

3.3.1 Population

Inclusion criteria were:

- Any patient 18 years or older,
- Currently taking an antibiotic for infection or having taken an antibiotic prescribed within the previous 48 hours of the time of capturing information.

The exclusion criteria were:

- Pregnant women on antibiotic treatment
- Patients who did not give consent

3.3.2 Sample and sampling

Patient records were selected using convenience sampling, which is a type of nonprobability sampling typically consisting of persons either known by the researchers and/or readily available to the investigators (Özdemir *et al.,* 2011). The sample size was determined to be a total of 350 for both stages of the study, as calculated by biostatisticians of the Faculty of Health Sciences Research Office, University of the Witwatersrand and based on the outcomes of a similar

study conducted in Egypt using an average number of patients admitted in each of the study wards per month, an α = 0.05 and power of 80% (Saied *et al.,* 2015).

3.3.3 Data collection

In both stages of the study the same variables were collected. In the first stage of the study, patient hospital numbers were extracted from the surgery department electronic discharge records and were used to retrieve files that were electronically scanned as portable document format (pdf) files on the hospital computers at the Hospital Information Management unit. Data on patient demographics, antibiotic utilisation, microbiology laboratory results and biomarkers were obtained. Laboratory results that could not be found in the patient's files were retrieved from NHLS database at the Microbiology Department. The data were captured on the data collection sheets (Appendices 2, 3 and 6) and later transferred to spreadsheets, and coded. However, in the second stage, the data were collected from the patient files in the ward after informed consent was obtained and the patients were then followed up until discharge to capture the remaining set of data. As in the first stage, for the laboratory investigations that were not present in the patient files, the NHLS database was also used to support and verify the microbiology records including inflammatory markers such as FBC, CRP and PCT that can be used to distinguished bacterial from acute viral respiratory infections (Mendelson, 2015a).

In both stages, patient's demographic characteristics and information on the diagnoses, type of surgery, and number of surgical procedures were captured. The data on antibiotic utilisation collected included the name of medicines, clinical indication for the use of antibiotics (prophylactic/empiric/targeted), doses, duration of therapy, route of administration, allergy and adverse reaction. For each patient receiving antibiotics, data on microscopy culture and sensitivity (MCS), type of specimen requested, type of bacteria cultured, susceptible, resistant and recommended antibiotic by microbiologist and whether the culture was sought before the commencement of antibiotics. The list of WHO assigned DDDs for drugs were obtained from the website of WHO Collaborating Centre for Drug Statistics and Methodology (WHO, 2016a).

- **DDD**

  The number of doses administered for each drug, the net quantity of drug administered to patients and WHO DDD was used to calculate the DDD for each drug. DDD is an internationally recognised unit of measurement of drug consumption (personal communication with the Director of the WHO Collaborating Centre for Drug Statistics Methodology Oslo – "Hanne Strøm" and other researchers who use this metric to determine the volume of antibiotic consumption in their studies were contacted for advice). The drug consumption in DDD/1000 patient days was also calculated by dividing DDD by the number of patient days in each stage of the study and then multiply by 1000.

$$Drug\ usage = \frac{Items\ issued\ \times\ Amount\ of\ drug\ per\ item}{WHO\ DDD}$$

$$Volume\ of\ drug\ consumption = \frac{DDDs}{Patient\ days} \times\ 1000$$

Patient days = ∑Date of discharge minus ∑date of admission

- **Cost**

  The price of medicines used by the patients in both stages was determined using the rate obtained from the central hospital pharmacy of the CMJAH and Master Price Catalogue (2015) list of the National Department of Health, in South African Rand (R) (Appendix 5). The prices were also converted to United State dollar (US$) to enable comparison of costs with other international studies. The utilisation of microbiological tests before the commencement of antibiotics or in the monitoring of treatment progress and use of other biological markers that change in response to bacterial infections were assessed. The microbiology and biomarker's results were also reviewed retrospectively from patient records and NHLS database (Appendix 6). The prices of laboratory investigations were obtained from the investigation price list of the NHLS tariffs (Appendix 7).

3.3.4 **Data categorisation**

- **Appropriateness of antibiotic utilisation**

  Antibiotics therapy can be inappropriate for several reasons at the same time, and the Gyssen's guideline provides a flat form to categorise inappropriate prescriptions into more than one sub-category from category ii to iv. The antibiotic prescription is regarded as inappropriate if prescribed for an improper dosage (sub-category iia), improper dosage interval (sub-category iib), and improper route (sub-category iic). Excessive duration of therapy (sub-category iiia), short duration of therapy (sub-category iiib), more effective alternative agent (iva), less toxic alternative drug (ivb), less expensive alternative antibiotic (ivc), less broad-spectrum alternative agent (ivd). Unjustified prescription (v) and insufficient information for categorisation (vi), category (i) represent appropriate prescription. Unlike other guidelines it also provides an avenue to classify further inappropriate prescription based on the development of toxicity to the prescribed medicines to using of broad-spectrum antibiotic when a narrow-spectrum is available. This is a validated guideline used in many previous studies as reported in (Akhloufi *et al.,* 2015); (Hadi *et al.,* 2008); (Willemsen *et al.,* 2007) and (Willemsen *et al.,* 2010).

- **Type of diagnoses**

  In consultation with experts in the field from the University of the Witwatersrand the following categories for patient diagnoses were grouped accordingly:

- Upper gastrointestinal cases; these included perforated peptic ulcer diseases, oesophageal carcinomas etc.
- Lower gastrointestinal cases; these included lower gastrointestinal bleeding, rectal carcinomas etc.
- Gallbladder, biliary tract and liver cases; these included acute cholangitis, cholecystitis, pyogenic liver abscesses, primary liver cell carcinomas etc.
- Pancreas, appendix and splenic cases; e.g. peri-pancreatic sepsis, appendicitis, overwhelming post-splenectomy sepsis.
- Vascular cases, e.g. ischemic vascular diseases, stab injuries.
- Other general surgery cases, e.g. hernias, intestinal obstruction, cutaneous abscesses.

- **Type of surgical procedures**

  The type of surgical procedures was also categorised based on the type of wound (Knight *et al.*, 2001):

- Clean surgery,
- Clean-contaminated surgery,
- Contaminated surgery,
- Dirty surgery,

- **Clinical indication for antibiotic therapy**

- Empiric: a presumptive use of antibiotics before the result of culture.
- Targeted: the use of antibiotics based on the results of culture.
- Prophylactic: the use of antibiotics during surgical procedures to prevent SSIs.
- Others: this involve the use of erythromycin to stimulate gastrointestinal motility in newly operated patients, or azithromycin as an anti-biofilm agent.

3.3.5 Data analysis

Data was analysed using Stata software version 14 (StataCorp, College Station, TX, USA). Descriptive analysis, as well as graphical representation and comparison tables were used to present the data. Continuous variables were presented as means and standard deviations where data was normally distributed, or median and interquartile ranges where data was not normally distributed. Differences in percentages were analysed using chi-square tests. An independent sample *t*-test was used to compare the cost, DDDs and DDD/1000 patient days, between two stages of the study where data was normally distributed, or a non-parametric test such as Wilcoxon signed rank sum test, and was used where data was not normally distributed. A binary logistic regression model was used to predict the factors responsible for appropriateness prescriptions. A p value of <0.05 was regarded as significant.

3.4 ETHICAL CONSIDERATION

3.4.1 Permission to conduct the study

Permission to conduct the study was sought from the University of the Witwatersrand Human Research Ethics Committee and approved as per study ethics, approval number is M151142 (Appendices 8 and 9). Approval was also obtained from the chief executive officer (CEO) of the CMJAH (Appendix 10)

and Head of the Surgery Department, (Appendix 11). Permission to conduct the study was also granted by the heads of the two wards after approval was granted by the CEO and the head of department. The protocol was approved by the University of the Witwatersrand Protocol Assessment committee (Appendix 12).

3.4.2 **Informed consent**

A written informed consent was sought from all the patients that participated in the intervention stage of the study as required by the ethics committee and hospital letter of permission to conduct the study (Appendix 13). Patients were also given an information sheet about the investigator and reasons for conducting the study; only three patients declined consent for their records to be reviewed (Appendix 14).

3.4.3 **Anonymity and confidentiality**

Patients' anonymity was adhered to throughout the study, any information that may reveal patient identity such as name and address were not recorded to ensure confidentiality. A unique study number was assigned to their records and the list of study numbers and patients record numbers are kept in a password protected data file and only accessible to my supervisors and me. No patient file was taken away from the facility during the study, and their identity will not be revealed when the study is reported or published.

CHAPTER FOUR: RESULTS

The results of the two stages of the study are presented to compare the outcomes of the stages by demographic characteristics followed by antibiotic utilisation, laboratory investigations, appropriateness of antibiotic utilisation and cost. A total of 476 patient records were evaluated in this study, of which 264 were in the baseline stage and 212 in the intervention stage.

4.1 DEMOGRAPHIC CHARACTERISTICS OF PATIENTS

4.1.1 Gender

Overall, there were on average four-fold more patients in the General Surgery Ward than the Vascular Ward and in the intervention stage, the proportion of patients was less in the General Surgery Ward (Tables 4.1 and 4.2). In both stages of the study there were more males than females, with a preponderance of males of 56.82% overall in the baseline stage and 53.77% in the intervention stages (Tables 4.1 and 4.2). The results of the Pearson's chi-square test showed that there is no statistically significant difference in gender between the baseline and intervention stages of the study ($X^2 = 0.44$, $p = 0.501$).

Table 4.1: Gender distribution of patients in the baseline stage.

	Type of Ward		
Gender	**Vascular Ward n (%)**	**General Surgery Ward n (%)**	**Total of both Wards n (%)**
Male	29 (54.72)	121 (57.35)	150 (56.82)
Female	24 (45.28)	90 (42.65)	114 (43.18)
Total	**53 (100.00)**	**211 (100.00)**	**264 (100.00)**

Table 4.2: Gender distribution of patients in the intervention stage.

	Type of Ward		
Gender	**Vascular Ward n (%)**	**General Surgical Ward n (%)**	**Total of both Wards n (%)**
Male	40 (60.61)	74 (50.68)	114 (53.77)
Female	26 (39.39)	72 (49.32)	98 (46.23)
Total	**66 (100.00)**	**146 (100.00)**	**212 (100.00)**

4.1.2 Age distribution

In both stages of the study, most patients fell within the age bracket of 36 to 75 years (Figures 4.1 and 4.2). In the baseline stage the averages age of patients were 56 and 43 years in Vascular and General Wards, respectively, while in the intervention stage the average ages of patients were 56 and 49 years in Vascular and General Wards, respectively. This show that patients in the intervention stage were slightly older than those in the baseline stage. An independent sample *t*-test was conducted to examine the differences between ages of the participants in the baseline and intervention stages of the study. The results indicated ages of study participants in the baseline stage (mean = 45.77 ± 16.81 years), and intervention stage (mean = 51.50 ± 15.91 years) were statistically significantly different ($p = 0.01 < 0.05$).

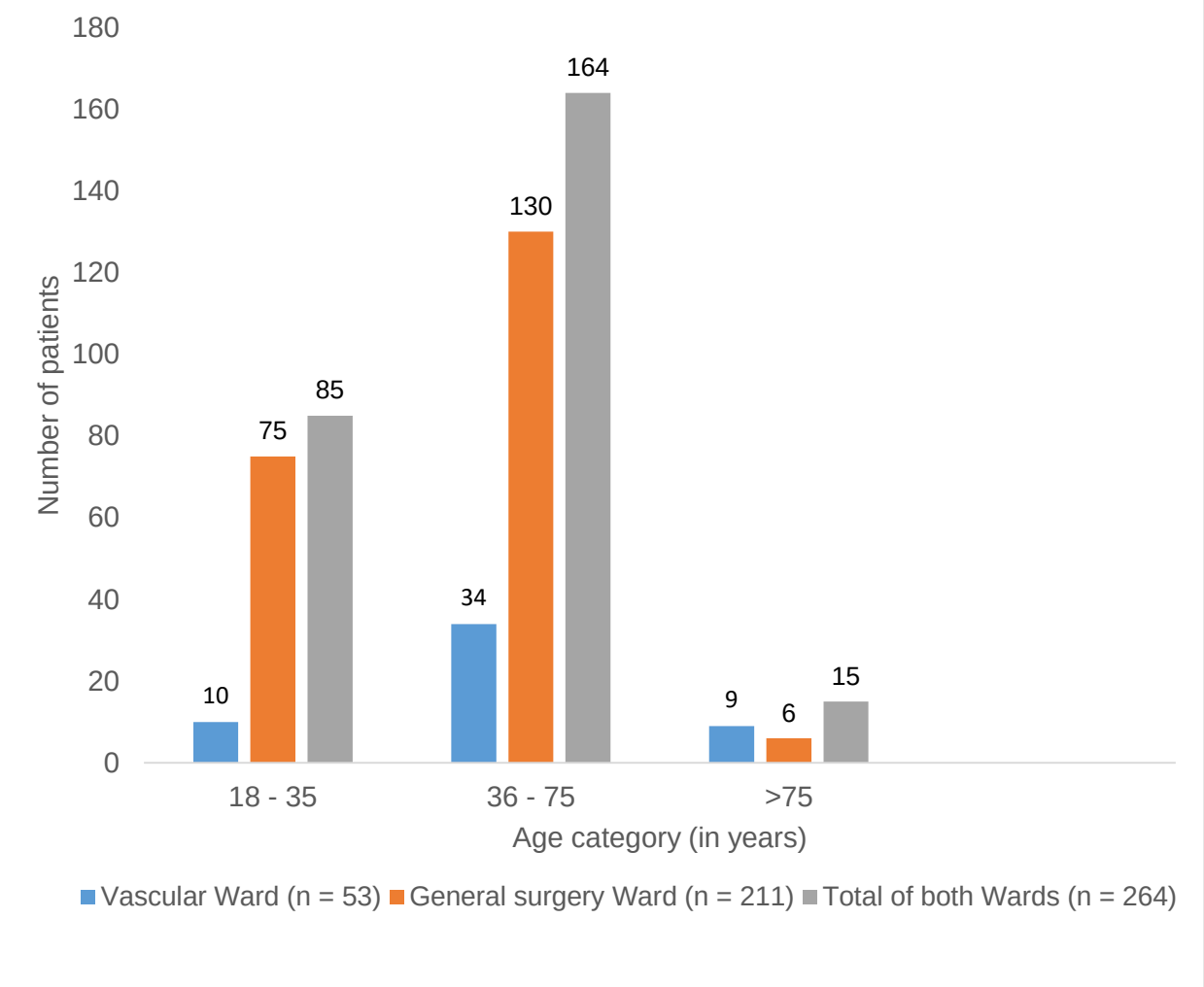

Figure 4.1: Patient age distribution in the baseline stage.

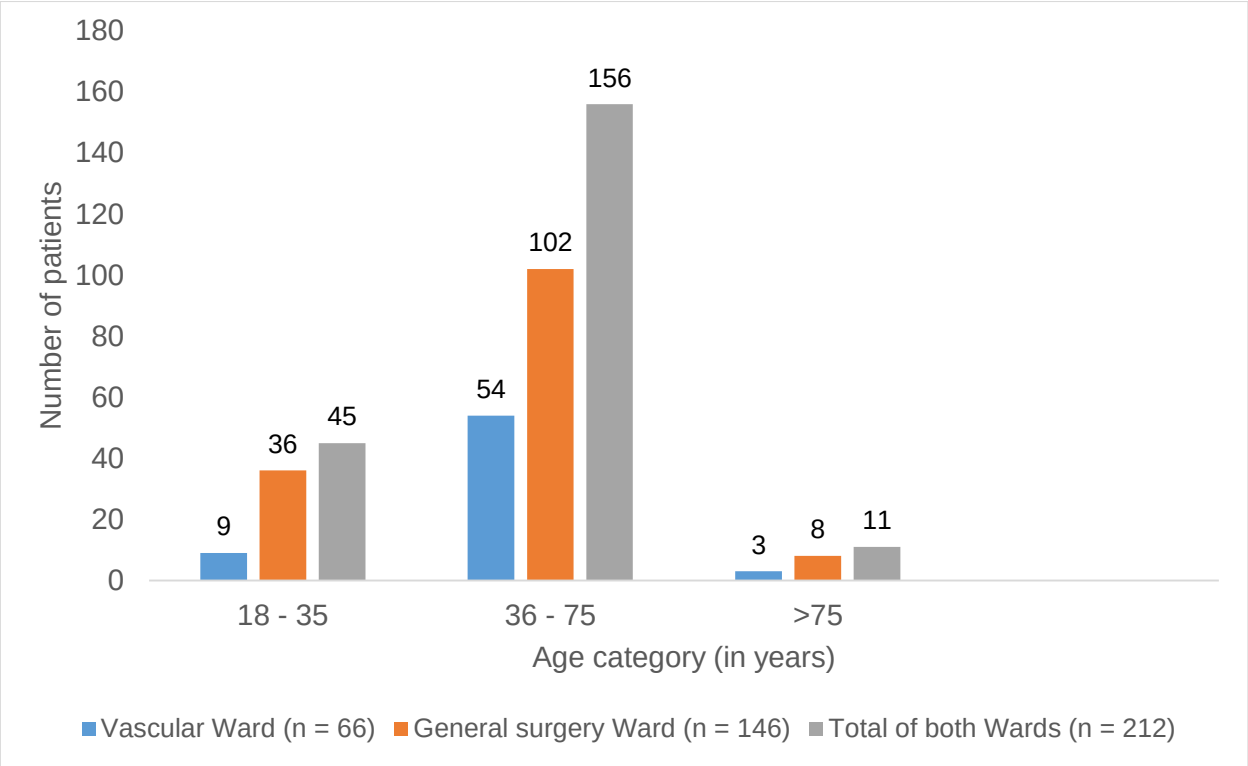

Figure 4.2: Patient age distribution in the intervention stage.

4.1.3 Hospital length of stay

In the baseline stage, the overall average Length of Stay (LOS) was 8.27 ± 9.52 days, while the average LOS in the Vascular and General Wards was 12.66 ± 10.03 and 7.16 ± 9.08 days, respectively. However, during the intervention stage, the average overall LOS was 13.23 ± 11.81 days, with 16.94 ± 15.44 and 11.55 ± 9.32 days as the average LOS in the Vascular and General Wards, respectively. An independent sample *t*-test was conducted to examine the differences between LOS of the participants in the baseline and intervention stages of the study. The results indicated that the LOS of the patients in the baseline stage (mean = 8.33 ± 9.58 days) and the intervention stage (mean = 13.44 ± 11.83 days) were statistically significantly different ($p = 0.01 < 0.05$).

4.1.4 Type of diagnoses

Lower gastrointestinal cases (LGCs) were the most common cases in the General Ward in the baseline stage 31%, while gallbladder, biliary tract and liver (GBLCs) 25%, in the intervention stage (Figures 4.3 and 4.4). In the Vascular Ward most of the patients had vascular cases comprising 89% and 91% in the baseline and the intervention stages, respectively (Figures 4.3 and 4.4). There

were few patients with non-vascular cases in Vascular Ward, and they were mostly transferred from the General Ward due shortage of bed space.

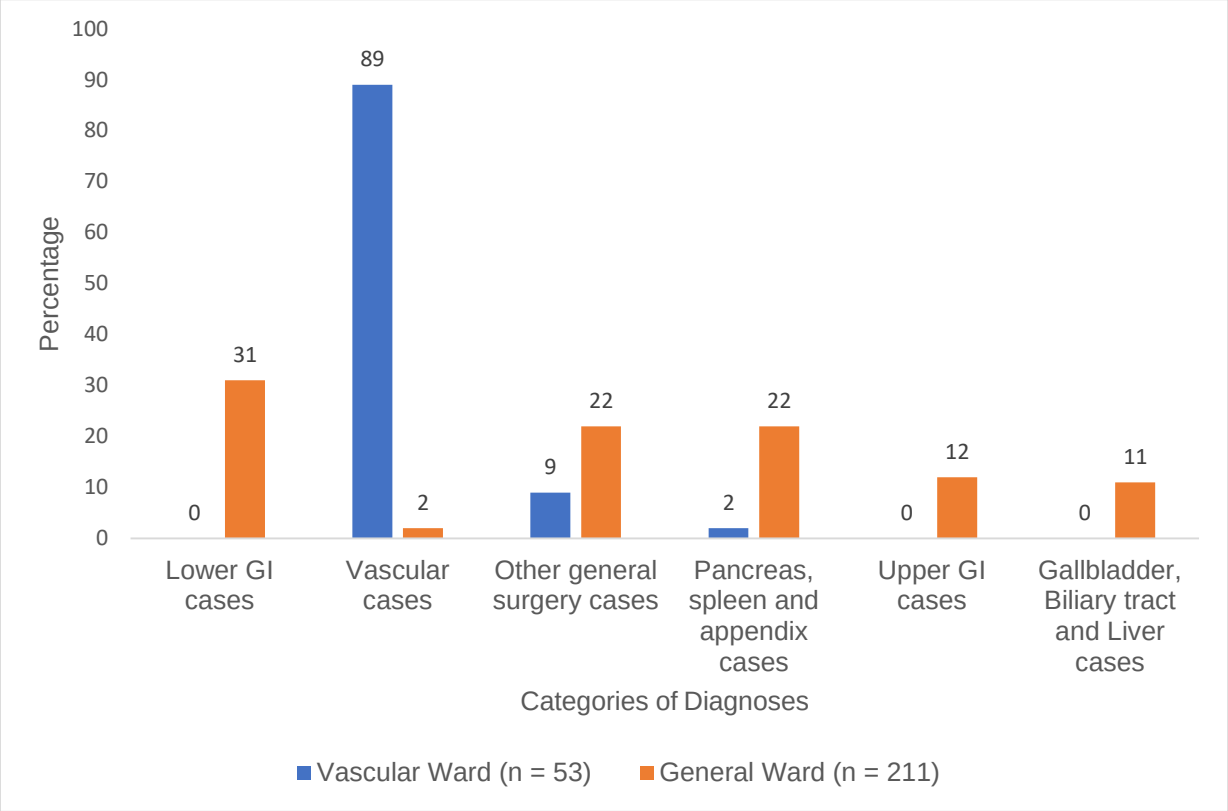

Figure 4.3: Categories of diagnoses in the baseline stage.

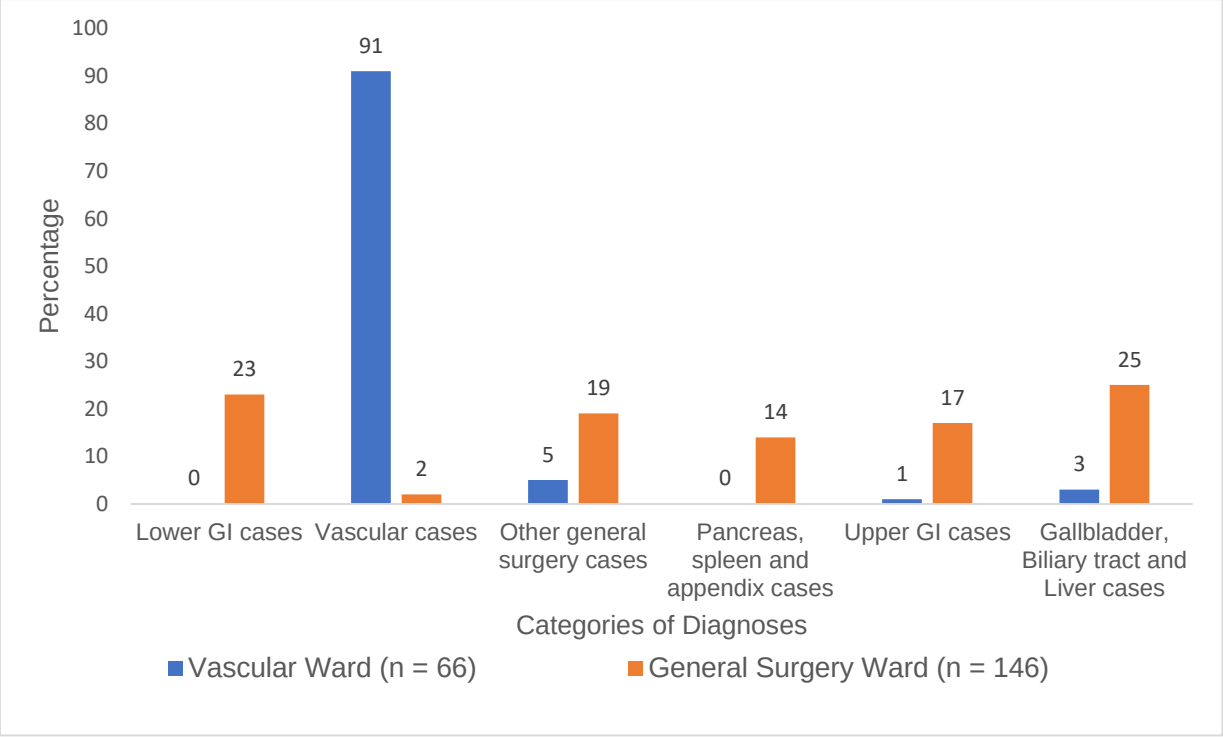

Figure 4.4: Categories of diagnoses in the intervention stage.

4.1.5 Classification of surgical procedures

In the baseline stage, most of the surgical operations were clean (40%) and dirty (40%) in the Vascular Ward, while in the General Ward contaminated surgeries (35%) were the most frequent type of surgical operations. However, during the intervention stage, in the Vascular Ward the majority of the patients had dirty surgical procedures (48%) (this is probably due to an increase in patients who had amputations), followed by clean surgical cases (26%). In the General Ward most of the cases were clean operations (34%) followed by those with contaminated surgeries (26%).

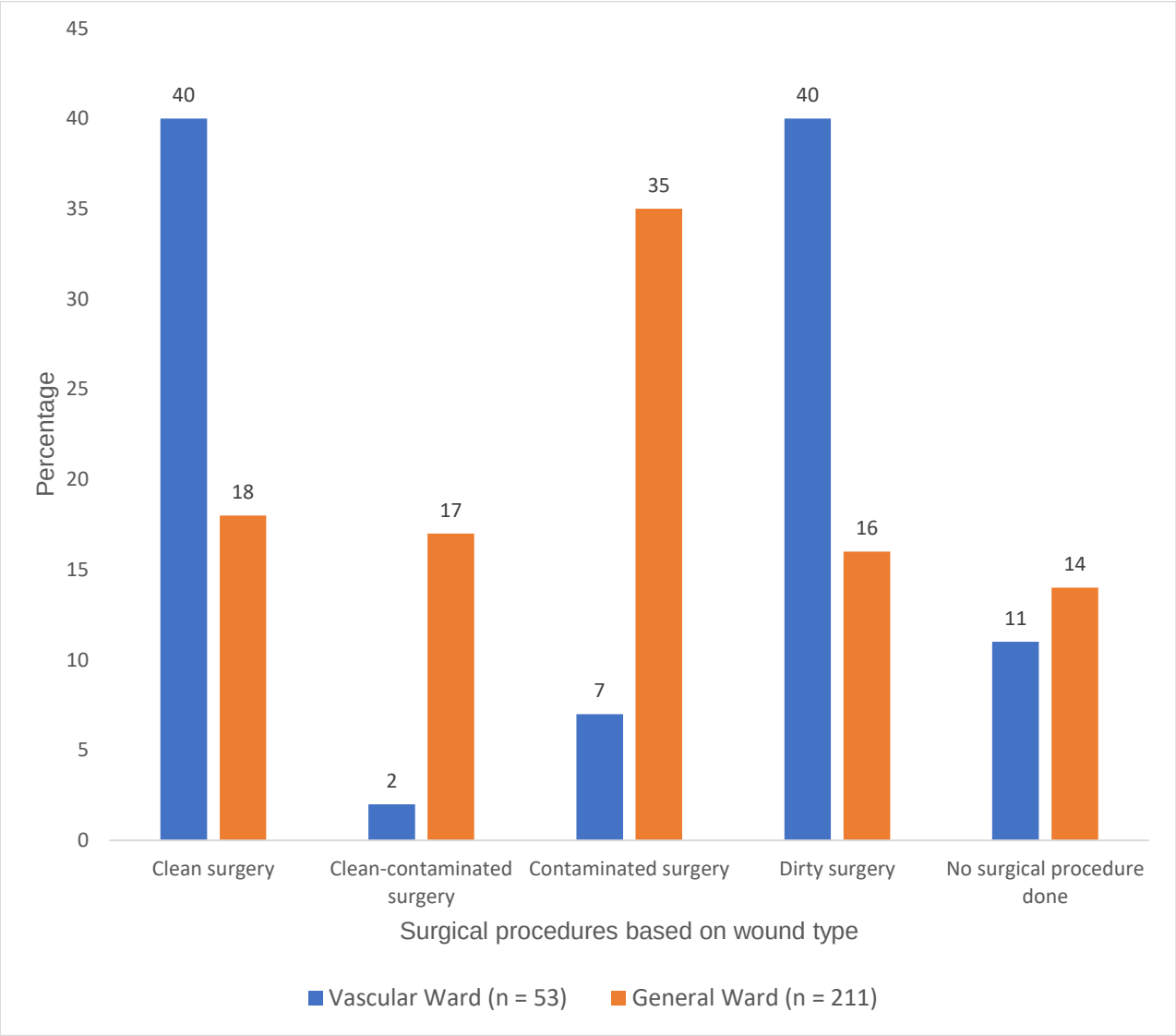

Figure 4.5: Surgery type based on type of surgical wound in the baseline stage.

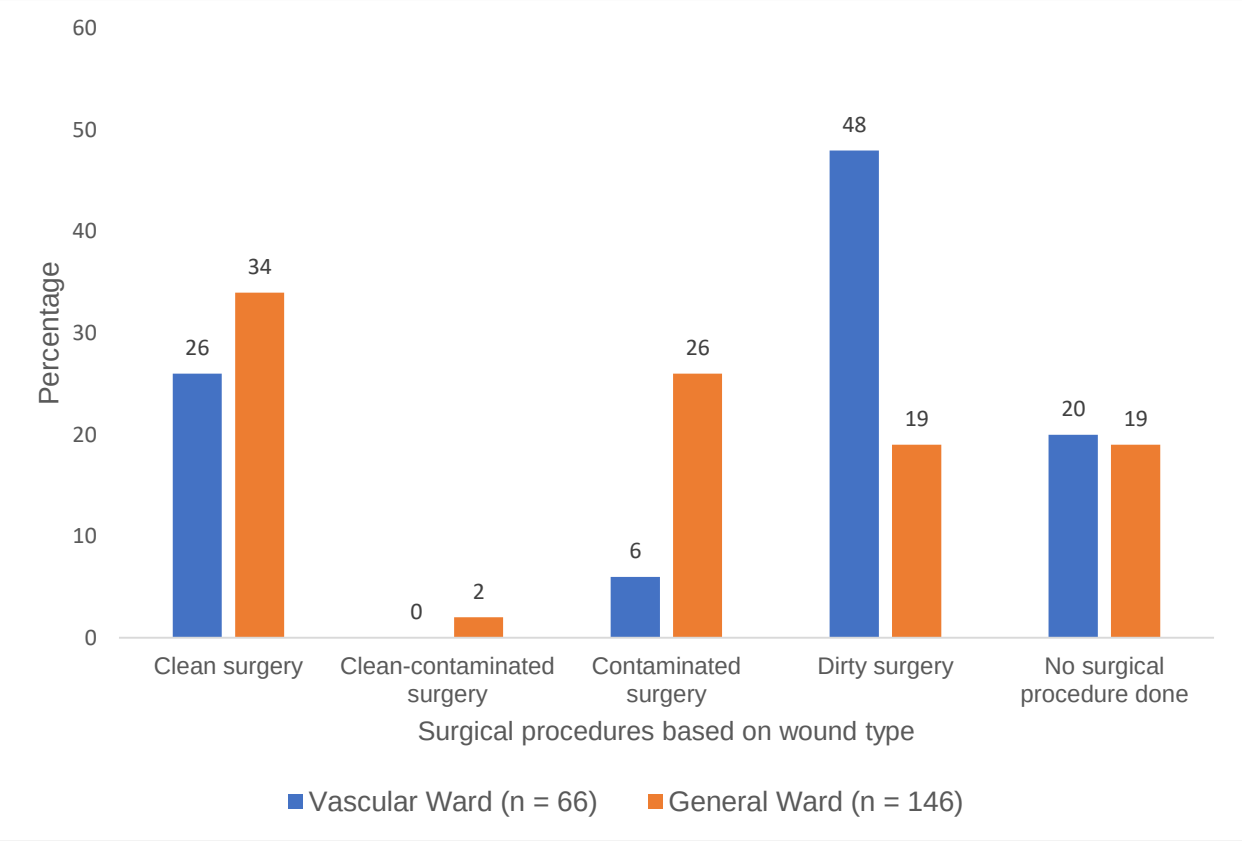

Figure 4.6: Surgery type based on type of surgical wound in the intervention stage.

4.1.6 Number of surgical procedures per stay

During the baseline stage, more than 90% of all the patients who were operated on had only a single procedure during their inpatient stay, while the remaining patients on average had either two or three procedures. In the intervention stage about 75% of the patients had a single procedure, 16.37% had two procedures, while the remainder had between three and five procedures (Tables 4.3 and 4.4).

Table 4.3: Number of surgical procedures per patient per stay in the baseline stage.

Number of Surgical Procedures	Vascular Ward n (%)	General Surgery Ward n (%)	Total of both Wards n (%)
One procedure	42 (85.71)	164 (92.66)	206 (91.15)
Two procedures	6 (12.25)	10 (5.65)	16 (7.08)
Three procedures	1 (2.04)	3 (1.69)	4 (1.77)
Total	**49 (100.00)**	**177 (100.00)**	**226 (100.00)**

Table 4.4: Number of surgical procedures per patient per stay in the intervention stage.

Number of Surgical Procedures	Vascular Ward n (%)	General Surgery Ward n (%)	Total of both Wards n (%)
One procedure	40 (75.47)	89 (75.42)	129 (75.44)
Two procedures	8 (15.09)	20 (16.95)	28 (16.37)
Three procedures	2 (3.77)	7 (5.93)	9 (5.26)
Four procedures	2 (3.77)	2 (1.69)	4 (2.34)
Five procedures	1 (1.89)	0 (0.00)	1 (0.58)
Total	**54 (100.00)**	**118 (100.00)**	**171 (100.00)**

4.2 ANTIBIOTIC UTILISATION

4.2.1 Number of antibiotics per patient per stay

In both stages of the study most of the patients had only one antibiotic per stay followed by those with two and three antibiotics and few patients had more than five antibiotics (Figures 4.7 and 4.8). In the baseline stage, there was a single patient who had a total of eleven antibiotics per stay due to sepsis and ICU admission (Figure 4.7). This patient was managed as a case of peri-pancreatic abscess with sepsis, spent 80 days on admission and had three surgical operations. More patients had a single agent in the General Ward of the baseline stage compared to the intervention stage, while in the Vascular Ward there were more patients that had one antibiotic in the intervention stage compared to baseline stage.

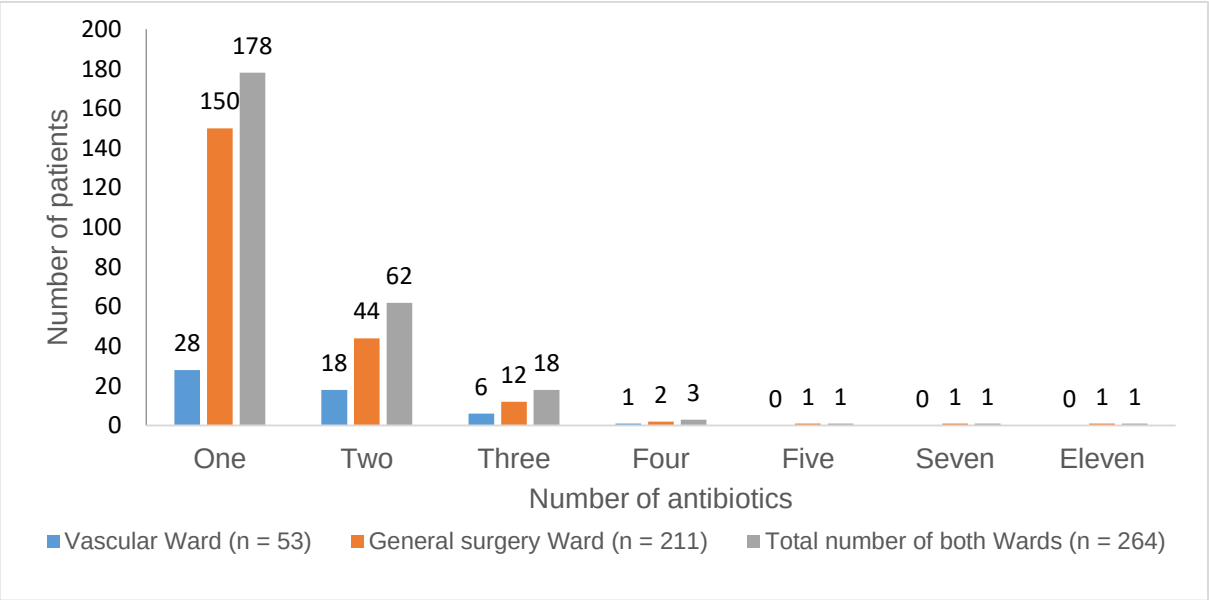

Figure 4.7: Number of antibiotics per patient per stay in the baseline stage.

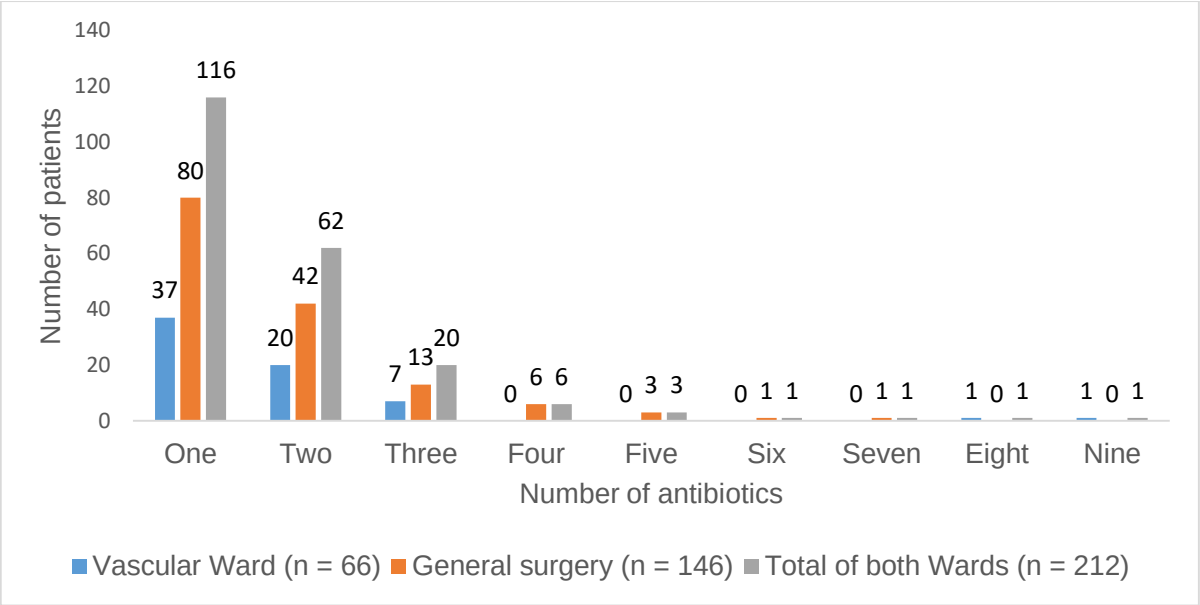

Figure 4.8: Number of antibiotics per patient per stay in the intervention stage.

4.2.2 Duration of antibiotic therapy

Overall, in the baseline stage 49.31% of patients received their antibiotic therapy for less than two days and 6.19% for more than seven days; while in the intervention stage 56.09% received their therapy between 2 to 7 days and only 2.07% had treatment for more than seven days. The overall average duration of therapy (DoTh), in the baseline stage was 2.62 ± 3.38 days, while in the Vascular and General Wards it was 2.83 ± 3.36 and 2.53 ± 2.66 days, respectively. During the intervention stage, the overall average duration was 2.49 ± 2.38 days, while in Vascular and General Wards it was 2.53 ± 2.66 and 2.47 ± 2.23 days, respectively (Tables 4.5 and 4.6). An independent sample *t*-test was conducted to examine the differences between the patients who had a duration of antibiotics therapy for two days and more between the two stages of the study. The results indicated that the duration of antibiotic therapy for two days and more in the baseline stage (mean = 4.74 ± 4.58 days) was statistically significantly greater ($p = 0.01 < 0.05$) than the intervention stage (mean = 3.96 ± 2.04 days). The classification of 2 days or more was also made in such a way to exclude those that were used for prophylaxis.

Table 4.5: Patients duration of antibiotic therapy in days' in the baseline stage.

Duration of Therapy	Vascular Ward n (%)	General Surgical Ward n (%)	Total of both Wards n (%)
0 - 1 day	48 (47.52)	167 (49.85)	215 (49.31)
2 - 7 days	44 (43.56)	150 (44.78)	194 (44.50)
>7 days	9 (8.91)	18 (5.35)	27 (6.19)
Mean duration of therapy	2.83 ± 3.36	2.56 ± 4.12	2.62 ± 3.96

Table 4.6: Patients duration of antibiotic therapy in days' in the intervention stage.

Duration of Therapy	Vascular Ward n (%)	General Surgical Ward n (%)	Total of both Wards n (%)
0 - 1 day	64 (44.76)	118 (40.41)	182 (41.84)
2 - 7 days	74 (51.75)	170 (58.22)	244 (56.09)
>7 days	5 (3.50)	4 (1.37)	9 (2.07)
Mean duration of therapy	2.53 ± 2.66	2.47 ± 2.23	2.49 ± 2.38

4.2.3 Clinical indications for the use of antibiotics

There was an overall increase in culture targeted therapy in both wards in the intervention stage (n = 88) compared to the baseline stage (n = 67), however the shift was not statistically significant (p = 0.125). In the General Ward, there was a reduction in empiric therapy from 186 prescriptions in the baseline stage to 158 prescriptions during the intervention stage. The "Others" category represents the use of macrolides such as erythromycin to stimulate gastrointestinal motility in patients who underwent abdominal surgery and azithromycin as an anti-biofilm agent (Figures 4.9 and 4.10).

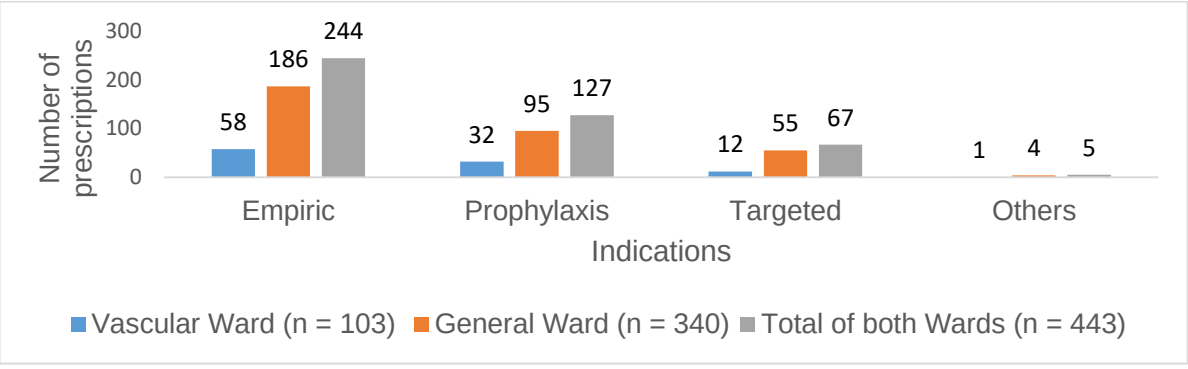

Figure 4.9: Antibiotic treatment based on clinical indications in the baseline stage.

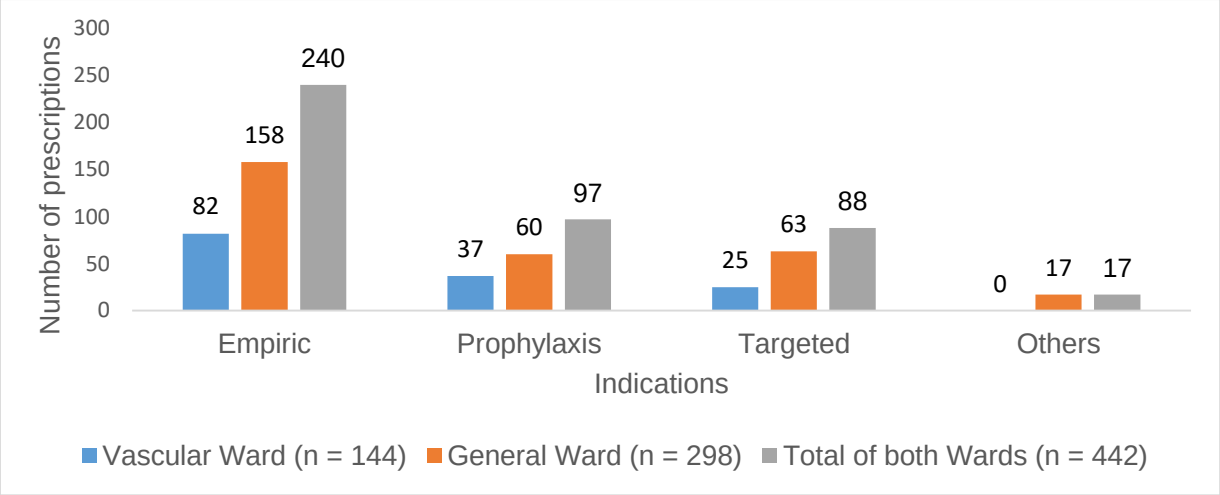

Figure 4.10: Antibiotic treatment based on clinical indications in the intervention stage.

4.2.4 Allergy to prescribed antibiotics

There were a few cases of allergy to prescribed drugs in both stages of the study, where penicillin allergy was the most common in both stages (Tables 4.7 and 4.8). Patients who had an allergy to penicillin presented with itching and skin rashes, it was stopped immediately and replaced with clindamycin. A patient who was found allergic to be sulphur in the intervention stage also presented with skin rashes and the drug was immediately stopped with no life threating symptoms. There was no proper documentation of symptoms among patients who were allergic to vancomycin in the baseline stage but the drug was stopped immediately.

Table 4.7: Allergy to prescribed drugs in the baseline stage.

Allergy	**Vascular Ward n (%)**	**General Surgical Ward n (%)**	**Total of both Wards n (%)**
Penicillin	3 (2.91)	2 (0.59)	5 (1.13)
Vancomycin	4 (3.88)	0 (0.00)	4 (0.90)
No allergy	96 (93.00)	338 (99.41)	434 (97.97)
Total	**103 (100.00)**	**340 (100.00)**	**443 (100.00)**

Table 4.8: Allergy to prescribed drugs in the intervention stage.

Allergy	**Vascular ward n (%)**	**General surgical ward n (%)**	**Total of both Wards n (%)**
Penicillin	3 (2.08)	8 (2.68)	11 (2.49)
Sulphur	0 (0.00)	1 (0.34)	1 (0.23)
No allergy	141 (97.92)	289 (96.98)	430 (97.29)
Total	**144 (100.00)**	**298 (100.00)**	**442 (100.00)**

4.2.5 **Route of drug administration**

The intravenous route of administration was the most utilised route in both stages of the study where 89.39% and 84.16% of all drugs were administered intravenously at baseline and in the intervention stage, respectively (Tables 4.9 and 4.10).

Table 4.9: Route of drug delivery in the baseline stage.

Route of Administration	**Vascular Ward n (%)**	**General Surgery Ward n (%)**	**Total of both Wards n (%)**
Intravenous	88 (85.45)	308 (90.59)	396 (89.39)
Oral	15 (14.56)	32 (9.41)	47 (10.61)
Total	**103 (100.00)**	**340 (100.00)**	**443 (100.00)**

Table 4.10: Route of drug delivery in the intervention stage.

Route of Administration	**Vascular Ward n (%)**	**General Surgery Ward n (%)**	**Total of both Wards n (%)**
Intravenous	125 (86.81)	247 (82.89)	372 (84.16)
Oral	19 (13.19)	51 (17.11)	70 (15.84)
Total	**144 (100.00)**	**298 (100.00)**	**442 (100.00)**

4.2.6 **Antibiotic prescriptions**

The average number of antibiotics per patient was 1.7 and 2.1 in the baseline and intervention stages, respectively. This show that more patient received combination therapy in the intervention stage, however this was mostly appropriate and sequentially administered. In the baseline stage amoxicillin/clavulanic acid was the most frequently used antibiotic (52.59%) followed by piperacillin/tazobactam (16.25%). During the intervention stage, though still the most used agent the frequency of amoxicillin/clavulanic reduced to (33.71%), while piperacillin/tazobactam increased to (26.02%) (Tables 4.11 and 4.12). Flucloxacillin is not accessible in South Africa, but was documented to have been used on one patient only in the baseline stage, where data was captured retrospectively. It could have been that flucloxacillin was written mistakenly instead of cloxacillin. However, the limitation here is that there is no opportunity to meet the patient and verify what was actually given as the data was captured retrospectively.

Table 4.11: Number of antibiotic prescriptions in the baseline stage.

Name of Antibiotics	ATC Codes	Number of Prescriptions	(%) of Total Prescriptions
Amoxicillin/Clavulanic acid	J01CR02	233	52.59
Piperacillin/Tazobactam	J01CR05	72	16.25
Cefazolin	J01DB04	36	8.13
Metronidazole	J01XD01	20	4.52
Fluconazole	J02AC01	13	2.93
Vancomycin	J01XA01	10	2.26
Cloxacillin	J01CF02	7	1.58
Imipenem	J01DH51	7	1.58
Ciprofloxacin	J01MA02	6	1.35
Sulfamethoxazole/Trimethoprim	J01EE01	5	1.13
Clarithromycin	J01FA09	5	1.13
Cefepime	J01DE01	4	0.90
Amoxicillin	J01CA04	4	0.90
Azithromycin	J01FA10	3	0.67
Clindamycin	J01FF01	3	0.68
Colistin	J01XB01	3	0.67
Amikacin	J01GB06	2	0.45
Ertapenem	J01DH03	2	0.45
Erythromycin	J01FA01	2	0.45
Gentamycin	J01GB03	2	0.45
Amphotericin B	J02AA01	1	0.23
Ceftazidime	J01DD02	1	0.23
Ceftriaxone	J01DD04	1	0.23
Flucloxacillin	J01CF05	1	0.23
Total		**443**	**100.00**

ATC Codes (Appendix 1) (WHO, 2016a).

Table 4.12: Number of antibiotic prescriptions in the intervention stage.

Name of Antibiotics	ATC Codes	Number of Prescriptions	(%) of Total Prescriptions
Amoxicillin/Clavulanic acid	J01CR02	149	33.71
Piperacillin/Tazobactam	J01CR05	115	26.02
Cefazolin	J01DB04	31	7.01
Fluconazole	J02AC01	19	4.3
Ertapenem	J01DH03	18	4.07
Metronidazole	J01XD01	18	4.07
Azithromycin	J01FA10	15	3.39
Ciprofloxacin	J01MA02	13	2.94
Clindamycin	J01FF01	12	2.71
Imipenem	J01DH51	8	1.81
Clarithromycin	J01FA09	7	1.58
Vancomycin	J01XA01	6	1.36
Amoxicillin	J01CA04	5	1.13
Cefepime	J01DE01	3	0.68
Cefotaxime	J01DD02	3	0.68
Cloxacillin	J01CF02	3	0.68
Nystatin	A07AA02	3	0.68
Sulfamethoxazole/Trimethoprim	J01EE01	3	0.68
Amikacin	J01GB06	2	0.45
Erythromycin	J01FA01	2	0.45
Meropenem	J01DH02	2	0.45
Ceftazidime	J01DD02	1	0.23
Ceftriaxone	J01DD04	1	0.23
Doxycycline	J01AA02	1	0.23
Gentamycin	J01GB03	1	0.23
Linezolid	J01XX08	1	0.23
Total		**442**	**100.00**

4.2.7 **Volume of antibiotic consumption**

In the baseline stage, a total of 1618.36 DDDs were prescribed compared to 1584.17 DDDs during the intervention stage, whilst a total of 739.30 DDDs/1000 patient days of antibiotics were consumed in the baseline stage compared to 564.93 DDDs/1000 patient days in the intervention stage (Table 4.13). During the baseline stage a total of 497.10 DDDs and 227.09 DDDs/1000 patient days of amoxicillin/clavulanic acid and 373.18 DDDs and 170.48 DDDs/patient days of piperacillin/tazobactam were utilised. While in the intervention stage a total of 375.16 DDDs and 133.80 DDDs/1000 patient days of amoxicillin/clavulanic acid

and piperacillin/tazobactam 330.43 DDDs and 117.84. DDDs/1000 patient days were consumed (Tables 4.13 and 4.14). An independent sample *t*-test indicated that there was no statistically significant difference between the baseline DDD and the intervention DDD $p = 0.92$. However, an independent sample *t*-test did show a statistically significant difference in the volume of antibiotic consumption measured in DDD per 1000 patient days between the baseline stage and intervention stage $p = 0.038$.

Table 4.13: Antibiotic consumption in the baseline stage.

Name of Antibiotics	ATC Codes	WHO DDD (g)	Total DDDs (95% CI)	DDD per 1000 Patient Days (95% CI)
Amoxicillin/ Clavulanic acid	J01CR02	3	497.10 (432.38 - 561.82)	227.09 (197.52 - 256.65)
Piperacillin/ Tazobactam	J01CR05	14	373.18 (185.12 - 561.24)	170.48 (84.57 - 256.39)
Cefazolin	J01DB04	3	17.50 (14.79 - 20.21)	7.99 (6.75 - 9.23)
Metronidazole	J01XD01	1.5	51.40 (24.28 - 78.52)	23.48 (11.09 - 35.87)
Fluconazole	J02AC01	0.2	296.00 (88.09 - 503.91)	135.22 (40.24 - 230.20)
Vancomycin	J01XA01	2	22.83 (4.16 - 41.50)	10.43 (1.90 - 18.96)
Cloxacillin	J01CF02	2	33.50 (17.98 - 49.02)	15.30 (8.22 - 22.39)
Imipenem	J01DH51	2	58.75 (24.51 - 92.99)	26.84 (11.19 - 42.48)
Ciprofloxacin	J01MA02	1	28.00 (9.31 - 46.69)	12.79 (4.25 - 21.33)
Sulfamethoxazole/ Trimethoprim	J01EE01	.	15.60 (5.32 - 25.88)	7.13 (2.43 - 11.82)
Clarithromycin	J01FA09	0.5	24.75 (11.56 - 37.94)	11.31 (5.28 - 17.33)
Cefepime	J01DE01	2	41.50 (10.99 - 72.01)	18.96 (5.02 - 32.89)
Amoxicillin	J01CA04	1	11.50 (4.26 - 18.74)	5.25 (1.94 - 8.56)
Azithromycin	J01FA10	0.5	27.00 (14.73 - 39.27)	12.33 (6.73 - 17.94)
Clindamycin	J01FF01	1.8	1.56 (-0.050 - 3.16)	0.71 (-0.02 - 1.45)
Colistin	J01XB01	3	33.00 (15.31 - 50.69)	15.08 (6.99 - 23.16)
Amikacin	J01GB06	1	5.37 (-4.53 - 15.26)	2.45 (-2.07 - 6.97)
Ertapenem	J01DH03	1	25.00 (-12.34 - 62.34)	11.42 (-5.64 - 28.48)
Erythromycin	J01FA01	2	8.25 (-0.10 - 16.60)	3.77 (-0.05 - 7.58)
Gentamycin	J01GB03	0.24	22.00 (2.35 - 41.65)	10.05 (1.07 - 19.03)
Amphotericin B	J02AA01	35mg	18.57	8.48
Ceftazidime	J01DD02	4	3.00	1.37
Ceftriaxone	J01DD04	2	1.00	0.46
Flucloxacillin	J01CF05	2	2.00	0.91
Total			1,618.36	739.30

Table 4.14: Antibiotic consumption in the intervention stage.

Name of Antibiotics	ATC Codes	WHO DDD (g)	Total DDDs (95% CI)	DDD per 1000 Patient Days (95% CI)
Amoxicillin/ Clavulanic acid	J01CR02	3	375.16 (310.04 - 438.68)	133.80 (110.57 - 156.45)
Piperacillin/ Tazobactam	J01CR05	14	330.43 (295.45 - 365.41)	117.84 (105.37 - 130.32)
Cefazolin	J01DB04	3	31 (17.52 - 44.48)	11.06 (6.25 - 15.86)
Fluconazole	J02AC01	0.2	323 (204.67 - 441.33)	115.19 (72.99 - 157.39)
Ertapenem	J01DH03	1	74 (53.79 - 94.20)	26.39 (19.19 - 33.59)
Metronidazole	J01XD01	2	42.07 (17.83 - 66.30)	15.00 (6.36 - 23.65)
Azithromycin	J01FA10	0.5	68.83 (44.06 - 93.61)	24.55 (15.71 - 33.38)
Ciprofloxacin	J01MA02	1	45 (31.47 - 58.53)	16.05 (11.22 - 20.88)
Clindamycin	J01FF01	1.8	49.67 (22.77 - 76.56)	17.71 (8.12 - 27.30)
Imipenem	J01DH51	2	20.63 (12.09 - 29.15)	7.36 (4.32 - 10.39)
Clarithromycin	J01FA09	1	42.50 (15.55 - 69.21)	15.16 (5.54 - 24.77)
Vancomycin	J01XA01	2	20.25 (1.19 - 39.31)	7.22 (0.42 - 14.02)
Amoxicillin	J01CA04	1	19.5 (7.83 - 31.17)	6.95 (2.79 - 11.11)
Cefepime	J01DE01	2	38.5 (10.93 - 66.07)	13.73 (3.89 - 23.56)
Cefotaxime	J01DD02	4	14.25 (12.78 - 15.72)	5.08 (4.56 - 5.61)
Cloxacillin	J01CF02	2	36.50 (3.79 - 69.21)	13.02 (1.35 - 24.68)
Nystatin	A07AA02	1.5	0.1	0.0
Sulfamethoxazole/ Trimethoprim	J01EE01	-	14.4 (11.13 - 17.67)	5.14 (3.97 - 6.30)
Amikacin	J01GB06	1	2 (0.03 - 3.97)	0.71 (0.01 - 1.41)
Erythromycin	J01FA01	2	3.75 (2.28 - 5.22)	1.34 (0.81 - 1.86)
Meropenem	J01DH02	2	6.25 (-5.05 - 17.55)	2.23 (-1.80 - 6.26)
Ceftazidime	J01DD02	4	3.25	1.16
Ceftriaxone	J01DD04	2	1.75	0.62
Doxycycline	J01AA02	0.1	12	4.28
Gentamycin	J01GB03	0.24	4.38	1.56
Linezolid	J01XX08	1.2	5	1.78
Total			1,584.17	564.93

4.2.8 **Most frequently utilised antibiotics**

The volumes of piperacillin/tazobactam consumed for empiric and culture directed therapy during the baseline stage were 147.57 and 22.91 DDDs/1000 patient days and 323.04 and 50.14 DDDs, respectively; compared to a lower utilisation of empiric (90.16 DDDs/1000 patient days and 252.80 DDDs) and increased culture-directed therapies (27.65 DDDs/1000 patient days and 77.62 DDDs) in the intervention stage (Tables 4.15 and 4.16). The consumption of

ertapenem increased during the intervention stage where 5.35 and 21.04 DDDs/1000 patient days and 15.00 and 59.00 DDDs were utilised for empiric and targeted purposes. In the baseline stage, 7.99 DDDs/1000 patient days and 17.5 DDDs of cefazolin were used for prophylactic purpose; while an increase was seen in the intervention stage to 11.06 DDDs/1000 patient days and 31.00 DDDs (Tables 4.15 and 4.16).

Table 4.15: DDDs and DDD/1000 patient days of the most frequently used antibiotics in the baseline stage.

Most Used Antibiotics	**Indication**		
	Prophylaxis (95% CI)	**Empiric (95% CI)**	**Targeted (95% CI)**
Total DDD by Antibiotics			
Amoxicillin/ Clavulanic acid	61.60 (47.41 - 75.79)	373.63 (322.07 - 425.19)	61.86 (42.06 - 81.67)
Cefazolin	17.5 (14.78 - 20.22)	-	-
Fluconazole	114.00	182.00 (107.56 - 256.44)	-
Metronidazole	0.33	42.60 (16.08 - 69.12)	8.47 (3.79 - 13.14)
Piperacillin/ Tazobactam	-	323.04 (135.42 - 510.66)	50.14 (32.99 - 67.30)
Total DDD per 1000 patient Days by Antibiotics			
Amoxicillin/ Clavulanic acid	28.14 (21.66 - 34.63)	170.69 (147.14 - 194.24)	28.26 (19.21 - 37.31)
Cefazolin	7.99 (6.75 - 9.24)	-	-
Fluconazole	52.08	83.14 (49.14 - 117.15)	-
Metronidazole	0.15	19.46 (7.35 - 31.57)	3.87 (1.73 - 6.00)
Piperacillin/ Tazobactam	-	147.57 (61.86 - 233.29)	22.91 (15.07 - 30.74)

Table 4.16: DDDs and DDD/1000 patient days of the most frequently used antibiotics in the intervention stage.

Most use Antibiotics	Indication		
	Prophylaxis (95% CI)	**Empiric (95% CI)**	**Targeted (95% CI)**
Total DDD by Antibiotics			
Amoxicillin/ Clavulanic acid	34.80 (23.68 - 45.92)	300.16 (251.68 - 348.63)	39.40 (19.96 - 58.84)
Cefazolin	31.00 (17.51 - 44.49)	-	-
Ertapenem	-	15.00 (10.05 - 19.95)	59.00 (39.17 - 78.83)
Fluconazole	34.00 (26.13 - 41.87)	223.00 (133.25 - 312.75)	66.00 (7.00 - 125.00)
Metronidazole	0.27	34.20 (11.02 - 57.38)	7.60 (-0.06 - 15.26)
Piperacillin/ Tazobactam	-	252.80 (222.59 - 283.02)	77.63 (60.40 - 94.85)
Total DDD per 1000 Patient Days by Antibiotics			
Amoxicillin/ Clavulanic acid	12.41 (8.45 - 16.38)	107.05 (89.76 - 124.33)	14.05 (7.12 - 20.98)
Cefazolin	11.06 (6.25 - 15.87)	-	-
Ertapenem	-	5.35 (3.58-7.11)	21.04 (13.97 - 28.11)
Fluconazole	12.13 (9.32 - 14.93)	79.53 (47.52 - 111.54)	23.54 (2.49 - 44.58)
Metronidazole	0.10	12.20 (3.93 - 20.46)	2.71 (-0.02 - 5.44)
Piperacillin/ Tazobactam	-	90.16 (79.30 - 100.93)	27.68 (21.54 - 33.83)

4.2.9 Comparison of average daily DDD to WHO DDD

In the baseline stage the average daily doses of the most frequently used drugs, prescribed for their empiric and targeted purposes such as IV amoxicillin/clavulanic acid and piperacillin/tazobactam appeared to have been used within the recommended WHO DDDs (Tables 4.17 and 4.18). While some of the less commonly used agents such as colistin and ertapenem which were used to treat multidrug resistant *A. baumannii*, CREs and *Pseudomonas* were used at high doses and for a long duration of 10 – 14 days, hence a high ratio. Other drugs with high ratios such as cloxacillin and fluconazole were also used for a longer duration. The intravenous ciprofloxacin was given at a high dose which resulted in high ratio. However, in the intervention stage the average daily consumption of IV amoxicillin/clavulanic acid, piperacillin/tazobactam and IV metronidazole were still within the recommended WHO recommended DDD. The less frequently used antibiotics such as ertapenem and cefepime were used for longer durations of 10 – 14 days to treat *Pseudomonas*, which resulted in a high ratio. Meropenem was used at doses higher than the WHO recommended DDD, while fluconazole was prophylactically used for a longer

duration which resulted in high ratio. The amikacin ratio appeared to be low in both stages, this could indicate wrong dosing although it was adjusted in some patients to as low as 400 – 500mg daily due to renal insufficiency. Also, the ratio of amphotericin was low and that of oral amoxicillin/clavulanic acid was high. The WHO DDD of gentamycin of 0.24g appears to be low (Tables 4.17 and 4.18).

Table 4.17: Average DDD/WHO DDD ratio in the baseline stage.

Name of Antibiotics	***Average Daily Dose (g)**	**WHO DDD (g)**	**DDDs Ratio (Average Daily Dose/WHO DDD)**
Amikacin	0.6	1	0.6
Amoxicillin	2.0	1	2.0
IV Amoxicillin/Clavulanic acid	3.3	3	1.1
Oral Amoxicillin/Clavulanic acid	1.8	1	1.8
Amphotericin B	10mg	35mg	0.3
IV Azithromycin	3.3	0.5	6.6
Oral Azithromycin	0.8	0.3	2.7
Cefepime	4.4	2	2.2
Ceftazidime	6.0	4	1.5
Ceftriaxone	2.0	2	1.0
IV Ciprofloxacin	0.8	0.5	1.6
Oral Ciprofloxacin	1.4	1	1.4
Clarithromycin	1.6	0.5	3.2
Clindamycin	0.9	1.8	0.5
Cloxacillin	3.4	2	1.7
Colistin	8.2mu	3mu	2.7
Ertapenem	1.8	1	1.8
Erythromycin	0.5	1	0.5
Flucloxacillin	4.0	0.2	3.0
Fluconazole	0.6	0.2	3.0
Gentamycin	0.9	0.24	3.8
Imipenem	3.5	2	1.8
IV Metronidazole	1.2	1.5	0.8
Oral Metronidazole	1.0	2	0.5
Piperacillin/Tazobactam	13.9	14	0.9
Sulfamethoxazole/Trimethoprim	-	-	-
Vancomycin	1.9	2	0.9

*Drugs used for empiric/targeted therapy, mu = million unit.

Table 4.18: Average DDD/WHO DDD ratio in the intervention stage.

Name of Antibiotics	*Average DDD (g)	WHO DDD (g)	DDDs Ratio (Average Daily DDD/WHO DDD)
Amikacin	0.5	1	0.5
Amoxicillin	1.8	1	1.8
IV Amoxicillin/Clavulanic acid	3.2	3	1.1
Oral Amoxicillin/Clavulanic acid	2.5	1	2.5
IV Azithromycin	0.9	0.5	1.8
Oral Azithromycin	0.3	0.3	1.0
Cefepime	4.0	2	2.0
Cefotaxime	2.5	4	0.6
Ceftazidime	3.3	4	0.8
Ceftriaxone	2.5	2	1.3
IV Ciprofloxacin	1.1	0.5	2.2
Oral Ciprofloxacin	0.8	1	0.8
IV Clarithromycin	0.8	1	0.8
Oral Clarithromycin	1.1	0.5	2.2
Clindamycin	1.7	1.8	0.9
Cloxacillin	5.2	2	2.6
Doxycycline	0.2	0.1	2.0
Ertapenem	1.8	1	1.8
Erythromycin	1.3	1	1.3
Fluconazole	0.7	0.2	3.2
Gentamycin	0.2	0.24	0.8
Imipenem	2.2	2	1.1
Linezolid	1.3	1.2	1.1
Meropenem	6.3	2	3.3
IV Metronidazole	1.5	1.5	1.0
Oral Metronidazole	1.2	2	0.6
Nystatin	0.0	1.5	0.0
Piperacillin/Tazobactam	14.1	14	1.0
Sulfamethoxazole/Trimethoprim	-	-	-
Vancomycin	0.8	2	0.4

*Drugs used for empiric and targeted therapy

4.3 UTILISATION OF LABORATORY INVESTIGATIONS

4.3.1 Prevalence of pathogens

In the baseline stage the most commonly cultured pathogens were *E. coli* (13.13%), *P. aeruginosa* (11.23%), *K. pneumoniae* (10.63%), and *A. baumannii* (9.38%) (Table 4.19). These were mostly isolated from specimens from the

General Ward. There were few fungal pathogens cultured and most of them were from General Ward. In contrast *P. aeruginosa* (13.94%), *K. pneumoniae* (11.06%), *E. coli* (10.58%), *A. baumannii* (7.21%) and *Enterococcus faecium* 7.21% were the most commonly isolated bacteria in the intervention stage and were mostly isolated from the General Ward (Tables 4.20). The prevalence of *C. difficile* infection among patients was 3.13% and 3.85% in baseline and intervention stages, respectively.

Table 4.19: Prevalence of pathogens in the baseline stage.

Cultured Pathogens	**Type of Ward**		**Total of both Wards n (%)**
	Vascular Ward n (%)	**General Surgical Ward n (%)**	
Escherichia coli	4 (16.00)	17 (12.59)	21 (13.13)
Pseudomonas aeruginosa	2 (8.00)	16 (11.85)	18 (11.23)
Klebsiella pneumoniae	-	17 (12.59)	17 (10.63)
Acinetobacter baumannii	4 (16.00)	11 (8.15)	15 (9.38)
methicillin-sensitive *Staphylococcus aureus*	1 (4.00)	11 (8.15)	12 (7.50)
Proteus mirabilis	2 (8.00)	9 (6.67)	11 (6.88)
Enterococcus faecalis	1 (4.00)	8 (5.92)	9 (5.63)
Enterococcus faecium	-	7 (5.18)	7 (4.38)
Clostridium difficile	1 (4.00)	4 (2.96)	5 (3.13)
coagulase-negative *Staphylococcus*	-	5 (3.70)	5 (3.13)
methicillin-resistant *Staphylococcus aureus*	4 (16.00)	-	4 (2.50)
Streptococcus agalactae	1 (4.00)	3 (2.22)	4 (2.50)
Staphylococcus epidermidis	-	4 (2.96)	4 (2.50)
Morganella morganii	-	3 (2.22)	3 (1.88)
Candida albicans	-	3 (2.22)	3 (1.88)
Enterobacter aerugenes	-	3 (2.22)	3 (1.88)
Candida glabrata	1 (4.00)	1 (0.74)	2 (1.25)
Bacillus specie	1 (4.00)	1 (0.74)	2 (1.25)
Candida parapsilosis	-	2 (1.5)	2 (1.25)
Streptococcus constellatus	-	2 (1.48)	2 (1.25)
Providentia rettgeri	-	2 (1.48)	2 (1.25)
Streptococcus anginosus	-	1 (0.74)	1 (0.63)
Streptococcus haemolyticus	-	1 (0.74)	1 (0.63)
Corynebacterium species	-	1 (0.74)	1 (0.63)
Prevotella bivia	-	1 (0.74)	1 (0.63)
Peptostreptococcus anaerobius	-	1 (0.74)	1 (0.63)
Clostridium perfringes	1 (4.00)	-	1 (0.63)
Klebsiella oxytoca	1 (4.00)	-	1 (0.63)
Micrococcus specie	-	1 (0.74)	1 (0.63)
Enterococcus cloacae	-	1 (0.74)	1 (0.63)
Trichosporon asashi	1 (4.00)	-	1 (0.63)
Total	**25 (100.0)**	**135 (100.0)**	**160 (100.00)**

Table 4.20: Prevalence of pathogens in the intervention stage.

Cultured Pathogens	Type of Ward		Total of both Wards n (%)
	Vascular Ward n (%)	General Surgical Ward n (%)	
Pseudomonas aeruginosa	11 (22.45)	18 (11.32)	29 (13.94)
Klebsiella pneumoniae	7 (14.29)	16 (10.06)	23 (11.06)
Escherichia coli	-	22 (13.84)	22 (10.58)
Enterococcus faecium	1 (2.04)	14 (8.81)	15 (7.21)
Acinetobacter baumannii	3 (6.12)	12 (7.55)	15 (7.21)
Coagulase-negative *Staphylococcus*	2 (4.08)	11 (6.92)	13 (6.25)
Enterococcus cloacae	2 (4.08)	9 (5.66)	11 (5.29)
Enterococcus faecalis	-	9 (5.66)	9 (4.33)
methicillin-sensitive *Staphylococcus aureus*	7 (14.29)	1 (0.63)	8 (3.85)
Candida albicans	1 (2.04)	7 (4.40)	8 (3.85)
Clostridium difficile	1 (2.04)	7 (4.40)	8 (3.85)
methicillin-resistant *Staphylococcus aureus*	3 (6.12)	2 (1.26)	5 (2.40)
Proteus mirabilis	1 (2.04)	4 (2.52)	5 (2.40)
Burkholderia cephacia	2 (4.08)	1 (0.63)	3 (1.44)
Citrobacter koseri	2 (4.08)	1 (0.63)	3 (1.44)
Streptococcus agalactae	-	2 (1.26)	2 (0.96)
Enterobacter aerugenes	-	2 (1.26)	2 (0.96)
Acinetobacter iwoffii	-	2 (1.26)	2 (0.96)
Bacteroides eggerthi	-	2 (1.26)	2 (0.96)
Serratia marcescens	-	2 (1.26)	2 (0.96)
Streptococcus gallolyticus	-	2 (1.26)	2 (0.96)
Trischosporon mucoides	-	2 (1.26)	2 (0.96)
Staphylococcus epidermidis	1 (2.04)	-	1 (0.48)
Candida glabrata	-	1 (0.63)	1 (0.48)
Streptococcus anginosus	-	1 (0.63)	1 (0.48)
Corynebacterium specie	-	1 (0.63)	1 (0.48)
Klebsiella oxytoca	-	1 (0.63)	1 (0.48)
Micrococcus species	-	1 (0.63)	1 (0.48)
Bacteroides thetaiotaomicron	-	1 (0.63)	1 (0.48)
Citrobacter braakii	1 (2.04)	-	1 (0.48)
Citrobacter freudii	1 (2.04)	-	1 (0.48)
Streptococcus mitis	1 (2.04)	-	1 (0.48)
Pseudomonas fluorescen	-	1 (0.63)	1 (0.48)
Haemophilus influenzae	1 (2.04)	-	1 (0.48)
Prevotella oralis	-	1 (0.63)	1 (0.48)
Achromobacter xylosoxidans	-	1 (0.63)	1 (0.48)
Stenotrophomonas maltophilia	-	1 (0.63)	1 (0.48)
Fusobacterium necrophorum	-	1 (0.63)	1 (0.48)
Gemella morbillorum	-	1 (0.63)	1 (0.48)
Total	**49 (100.00)**	**159 (100.00)**	**208 (100.00)**

4.3.2 Multi-drug resistant pathogens

Overall, 40 cases of multi-drug resistant pathogens were cultured in the baseline stage compared to 62 in the intervention stage. In both stages of the study Gram-negative bacteria were the most common bacteria that showed resistance to most classes of antibiotics. Some of these were MRSA requiring the use of vancomycin, and of the *enterococci* some were VREs. Most of the *Enterobacteriaceae* were ESBLs, while almost all the *Klebsiella pneumoniae* were carbapenemase producers. Most of these pathogens were cultured from specimens of the General Ward (Tables 4.21 and 4.22). In the baseline stage *Acinetobacter baumannii* (20.00%), *Klebsiella pneumoniae* (17.50%) and *Enterococcus faecium* (12.50%) were the most common resistant bacteria while in the intervention stage, *Klebsiella pneumoniae* (22.58%), *Enterococcus faecium* (20.97%), and *Acinetobacter baumannii* (19.35%) were the most common bacterial pathogen causing resistance. In the baseline stage, most of the resistant organisms were isolated from urine samples (25%) and were mostly from the General Ward, followed by blood (20%) and superficial swabs 17.5% (Appendix 15). During the intervention stage, resistant organisms were mainly isolated from fluid/tissue (50%) and superficial swabs (21%) (Appendix 16).

Table 4.21: Pattern of multi-drug resistant bacteria in the baseline stage.

Resistant Pathogens	**Type of Ward**		**Total of both Wards n (%)**
	Vascular Ward n (%)	**General Surgical Ward n (%)**	
Acinetobacter baumannii	2 (25.00)	6 (18.75)	8 (20.00)
Klebsiella pneumoniae	-	7 (21.88)	7 (17.50)
Enterococcus faecium	-	5 (15.63)	5 (12.50)
Escherichia coli	1 (12.50)	3 (9.38)	4 (10.00)
methicillin-resistant *Staphylococcus aureus*	4 (50.00)	-	4 (10.00)
Enterococcus faecalis	1 (12.50)	2 (6.25)	3 (7.50)
Staphylococcus epidermidis	-	3 (9.38)	3 (7.50)
Pseudomonas aeruginosa	-	2 (6.25)	2 (5.00)
Enterobacter aerugenes	-	2 (6.25)	2 (5.00)
Streptococcus haemolyticus	-	1 (3.1)	1 (2.50)
Morganella morganii	-	1 (3.13)	1 (2.50)
Total	**8 (100.00)**	**32 (100.00)**	**40 (100.00)**

Table 4.22: Pattern of multi-drug resistant bacteria in the intervention stage.

Resistant Pathogens	Type of Ward		Total of both Wards n (%)
	Vascular Ward n (%)	General Surgical Ward n (%)	
Klebsiella pneumoniae	4 (33.33)	10 (20)	14 (22.58)
Enterococcus faecium	1 (8.33)	12 (24)	13 (20.97)
Acinetobacter baumannii	2(16.67)	10 (20.00)	12 (19.35)
Escherichia coli	-	6 (12.00)	6 (9.68)
methicillin-resistant *Staphylococcus aureus*	4 (33.34)	2 (4.00)	6 (9.68)
Pseudomonas aeruginosa	-	4 (8)	4 (6.45)
Burkholderia cephacia	1 (8.33)	1 (2)	2 (3.23)
Enterococcus faecalis	-	1 (2)	1 (1.61)
Enterococcus cloaclae	-	1 (2)	1 (1.61)
Acinetobacter iwoffii	-	1 (2)	1 (1.61)
Serratia marcescens	-	1 (2)	1 (1.61)
Achromobacter xylosoxidans	-	1 (2)	1 (1.61)
Total	**12 (100.00)**	**50 (100.00)**	**62 (100.00)**

4.3.3 Classification of cultured pathogens

In the Vascular Ward of the baseline stage, 23% of the cultured pathogens were either mixed isolates or normal flora, this high yield of polymicrobial organisms suggested a high collection of superficial swabs (Figures 4.11 and 4.12). Gram-negative bacteria were the most common isolates in the Vascular (42%) and General (55%) Wards. Similarly, in the intervention stage, Gram-negative bacteria were the most prevalent bacteria with a prevalence of 56% and 54% in the Vascular and General Wards, respectively. There was a reduction of normal flora/mixed isolate bacteria especially in the Vascular Ward from 23% in the baseline stage to 11% in the intervention stage, and this is probably due to increases in the collection of tissue specimens in the intervention stage (Figures 4.11 and 4.12).

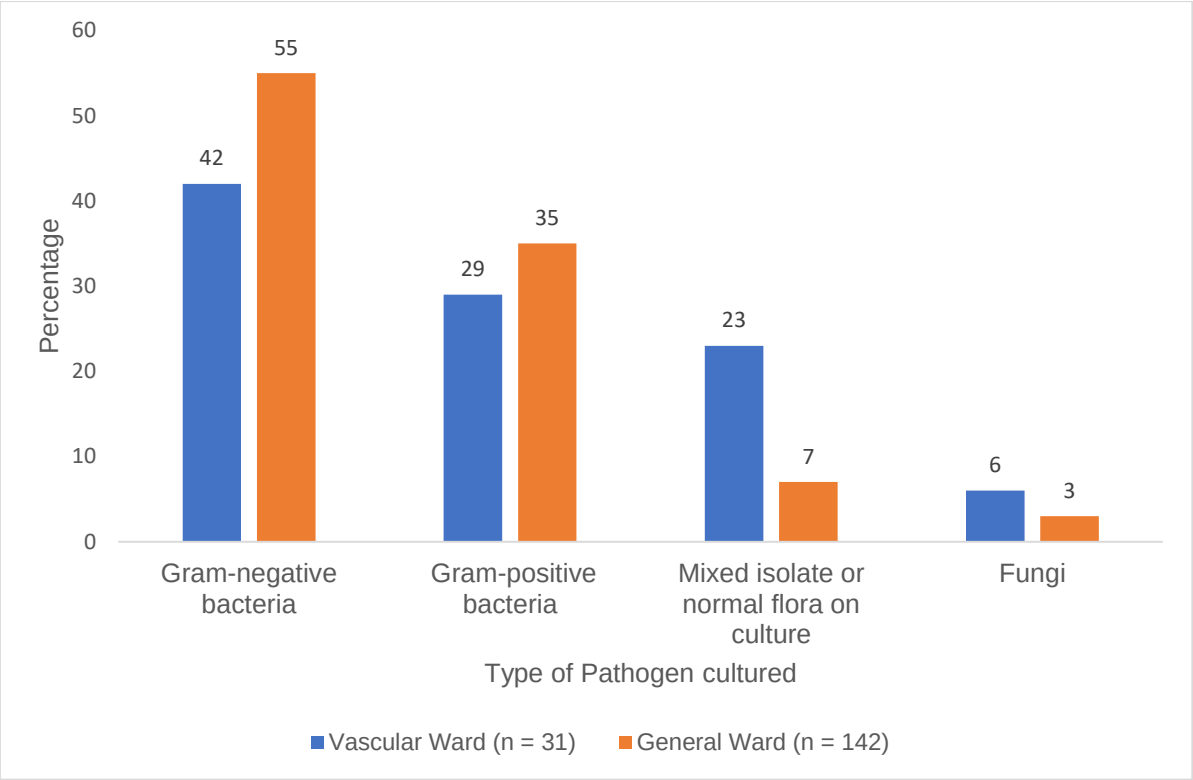

Figure 4.11: Nature of cultured pathogens in the baseline stage.

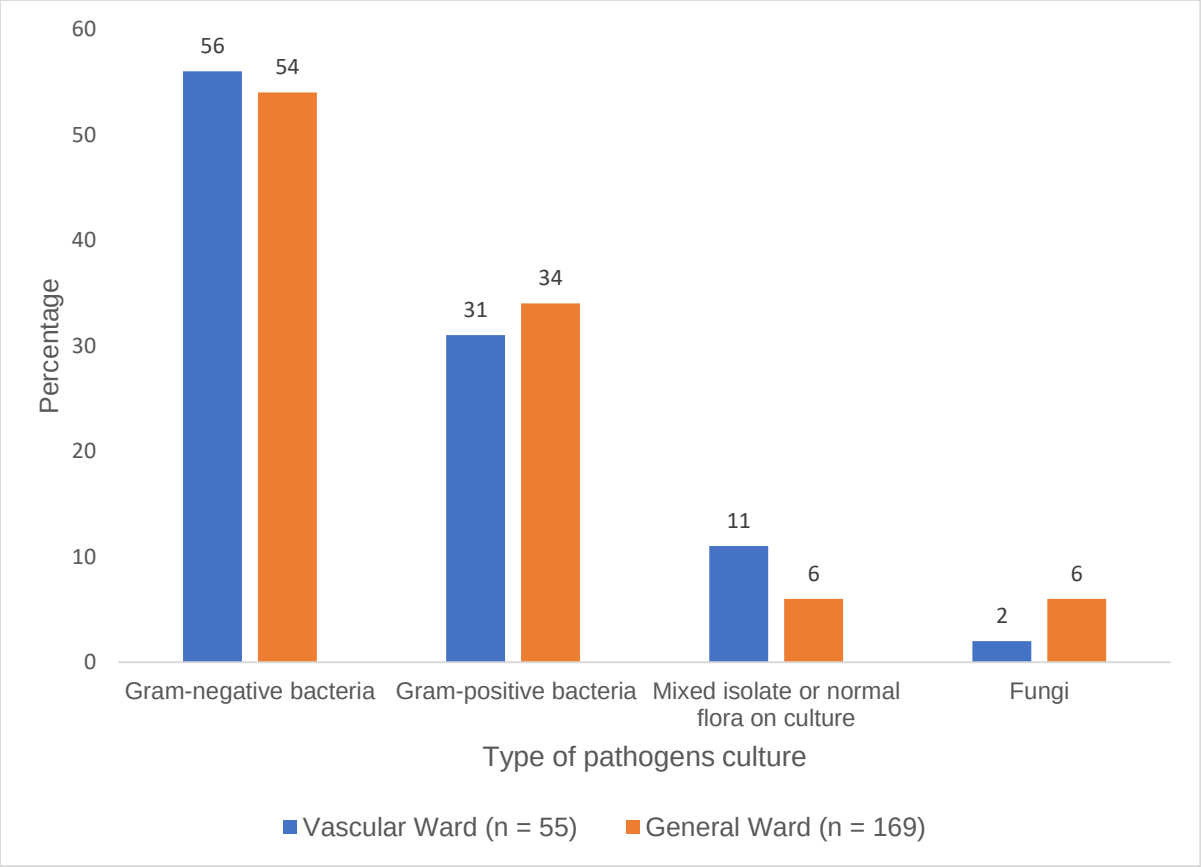

Figure 4.12: Nature of cultured pathogens in the intervention stage.

4.3.4 Timing of culture request

Overall, in the baseline stage of the study, only 22.16% of the cultures were requested before the commencement of antibiotics, while in the intervention stage only 24.20% of the cultures were requested before the commencement of antibiotics (Tables 4.23 and 4.24).

Table 4.23: Time of request culture in the baseline stage.

Time when Culture was Requested	Vascular Ward n (%)	General Surgery Ward n (%)	Total of both Wards n (%)
Culture requested to monitor disease progression	24 (36.92)	131 (39.46)	155 (39.04)
Culture requested 2 – 3 days after commencement of antibiotic	27 (41.54)	127 (38.25)	154 (38.79)
Culture requested before commencement of antibiotic	14 (21.54)	74 (22.29)	88 (22.16)
Total	**65 (100.00)**	**332 (100.00)**	**397 (100.00)**

Table 4.24: Time of request culture in the intervention stage.

Time when Culture was Requested	Vascular Ward n (%)	General Surgery Ward n (%)	Total of both Wards n (%)
Culture requested to monitor disease progression	65 (58.56)	158 (43.89)	223 (47.35)
Culture requested 2 – 3 days after commencement of antibiotic	27 (24.32)	107 (29.72)	134 (28.45)
Culture requested before commencement of antibiotic	19 (17.11)	95 (26.39)	114 (24.20)
Total	**111 (100.00)**	**360 (100.00)**	**471 (100.00)**

4.3.5 Nature of specimens collected for culture

In the baseline stage, the most commonly requested specimens for culture were blood (23.87%), urine (22.36%) and fluid/tissue (15.32%); while in the intervention stage fluid/tissue (28.81%), blood (27.75%) and urine (16.53%) were requested (Tables 4.25 and 4.26). The request of superficial swabs for culture in the Vascular Ward reduced from (22.73%) in the baseline stage to (11.16%) in the intervention stage.

Table 4.25: Specimens collected in the baseline stage.

Specimens	Type of Ward		Total of both Wards n (%)
	Vascular Ward n (%)	General Surgical Ward n (%)	
Blood	11 (16.67)	84 (25.30)	95 (23.87)
Urine	16 (24.24)	73 (21.99)	89 (22.36)
Fluid/Tissue	13 (19.72)	48 (14.45)	61 (15.32)
Superficial swab	15 (22.73)	39 (11.74)	54 (13.57)
Abscess	5 (7.58)	23 (6.93)	28 (7.04)
Stool	1 (1.52)	27 (8.13)	28 (7.04)
Sputum	4 (6.06)	20 (6.02)	24 (6.03)
Drain fluid (sterile cavity)	-	8 (2.41)	8 (2.01)
Drain fluid	1 (1.52)	5 (1.51)	6 (1.51)
Tracheal aspirate	-	4 (1.20)	4 (1.01)
Cerebrospinal fluid	-	1 (0.30)	1 (0.25)
Total	**66 (100.00)**	**332 (100.00)**	**398 (100.00)**

Table 4.26: Specimens collected in the intervention stage.

Specimens	Type of Ward		Total of both Wards n (%)
	Vascular Ward n (%)	General Surgical Ward n (%)	
Fluid/Tissue	30 (26.79)	106 (29.44)	136 (28.81)
Blood	32 (28.57)	99 (27.50)	131 (27.75)
Urine	27 (24.11)	51 (14.17)	78 (16.53)
Superficial swab	13 (11.61)	36 (10.0)	49 (10.38)
Stool	4 (3.57)	34 (9.44)	38 (8.05)
Sputum	6 (5.36)	18 (5.0)	24 (5.08)
Drain fluid (sterile cavity)	-	15 (4.17)	15 (3.18)
Cerebrospinal fluid	-	1 (0.28)	1 (0.21)
Total	**112 (100.00)**	**360 (100.00)**	**472 (100.00)**

4.4 APPROPRIATENESS OF ANTIBIOTIC UTILISATION AND SURGICAL PROPHYLAXIS

In this study the appropriateness of prescription was determined according to the Gyssen's guidelines (Appendix 4) and it was analysed by the categories of prophylaxis, empiric or targeted and overall. The appropriateness of surgical prophylaxis was based on the recommendations of the SAASP (Wasserman *et al.,* 2014) and Standard Treatment Guidelines and Essential Medicines Lists for South Africa (NDoH, 2015).

4.4.1 Appropriateness of all antibiotic prescriptions

In the baseline stage of the study 33% and 35% of all antibiotic prescriptions were inappropriate in the Vascular and General Wards, and overall 35% of antibiotic utilisation in this stage was inappropriate (Figure 4.13). However, in the intervention stage, 28% and 25% of prescriptions in the Vascular and General Wards were measured as inappropriate, while overall 26% of all antibiotics prescription were inappropriate (Figure 4.14). There is a statistically significant difference in appropriateness of all antibiotic prescriptions between the two stages of the study (p = 0.006).

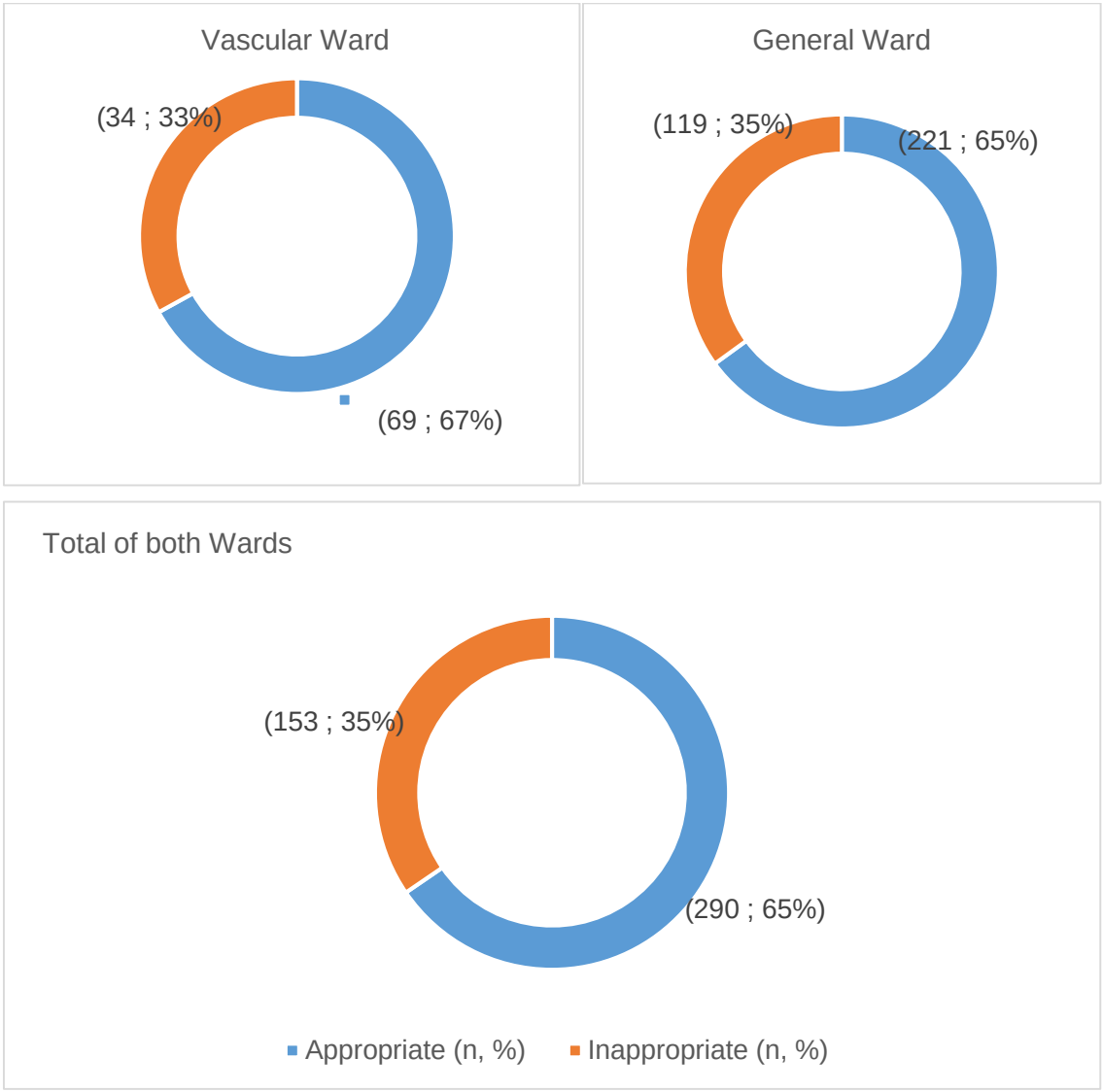

Figure 4.13: Appropriateness of antibiotic utilisation in the baseline stage.

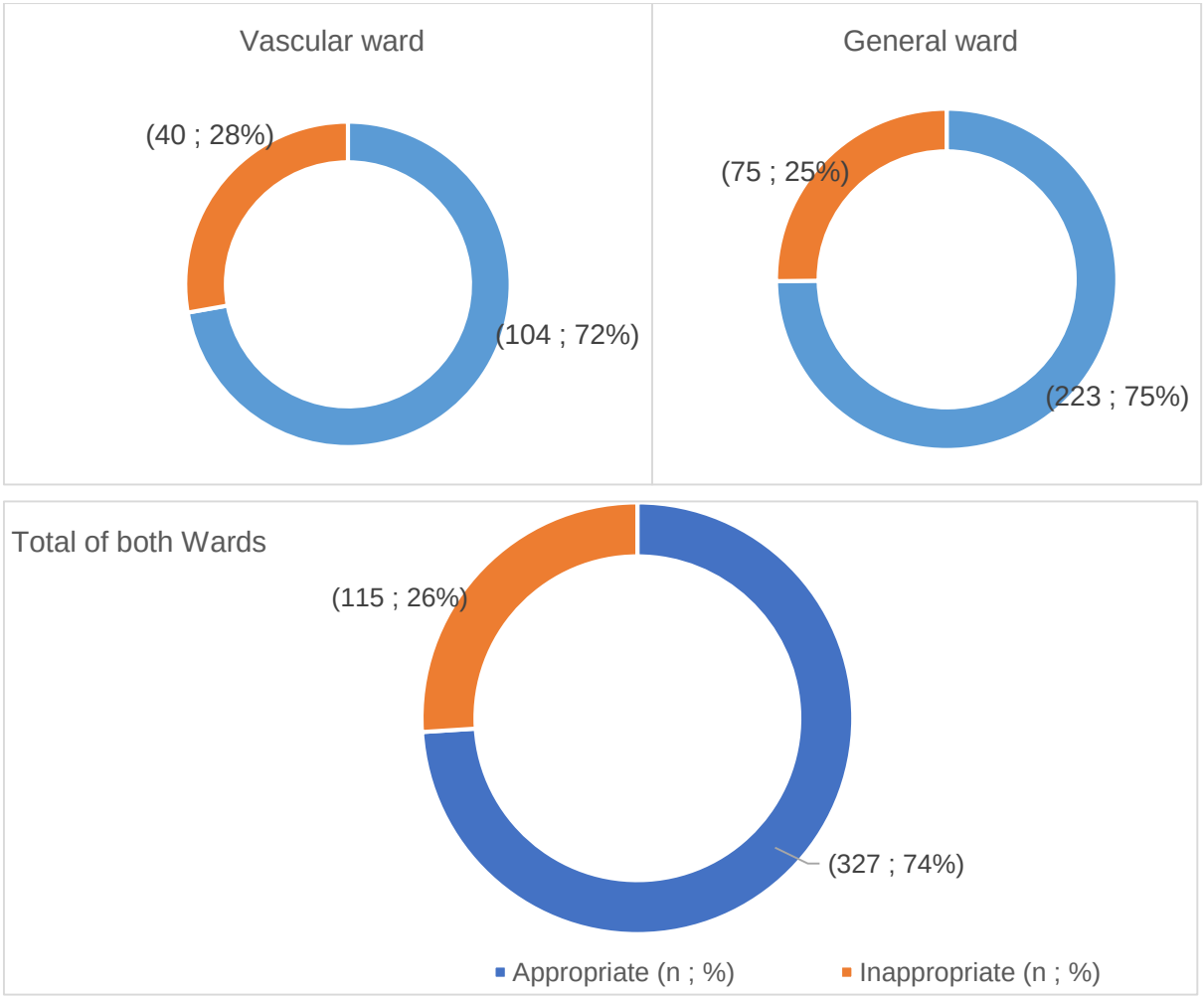

Figure 4.14: Appropriateness of antibiotic utilisation in the intervention stage.

4.4.2 Categories of inappropriate prescriptions

In the baseline stage, the main reasons for inappropriate prescriptions were due to use of less effective agents (27%), unjustified prescription (22%) and use of more broad-spectrum/more expensive agents (21%) where less broad-spectrum and less expensive agents were available (Figure 4.15). In the intervention stage, the use of less effective agents (40%), use of more expensive agents (17%) and unjustified prescription (14%) were the major causes of inappropriate utilisation (Figure 4.16).

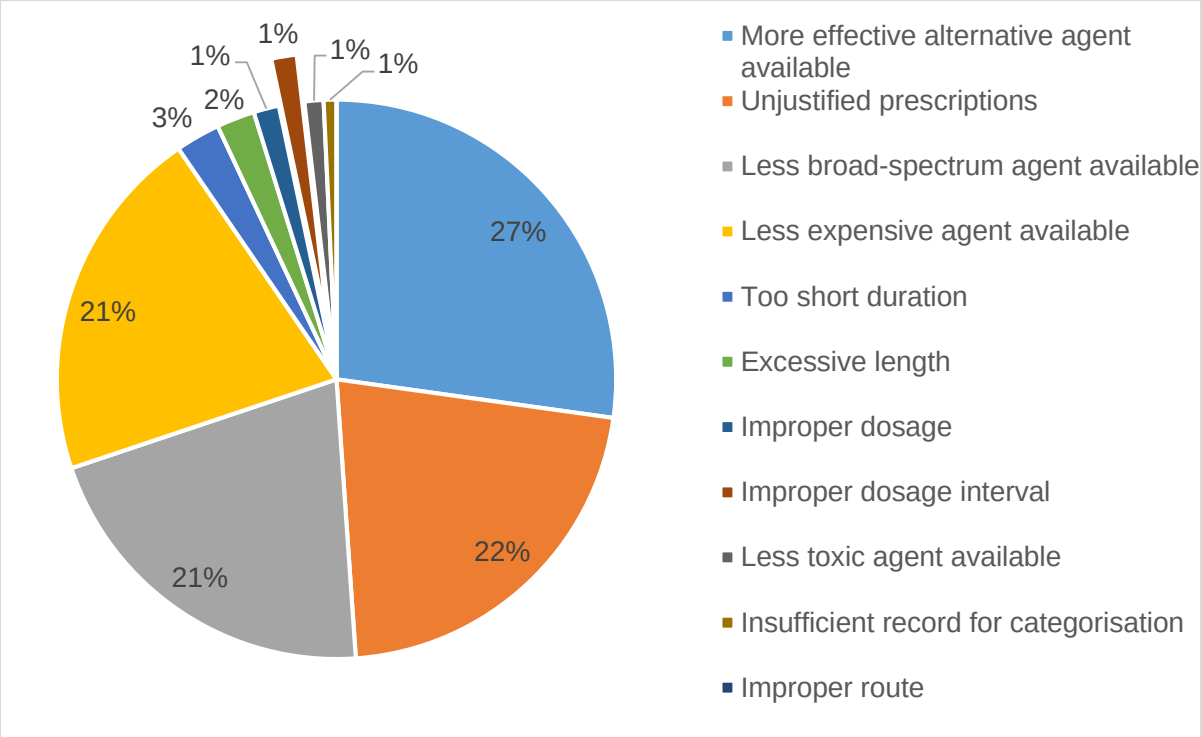

Figure 4.15: Categories of inappropriate antibiotic utilisation in the baseline stage.

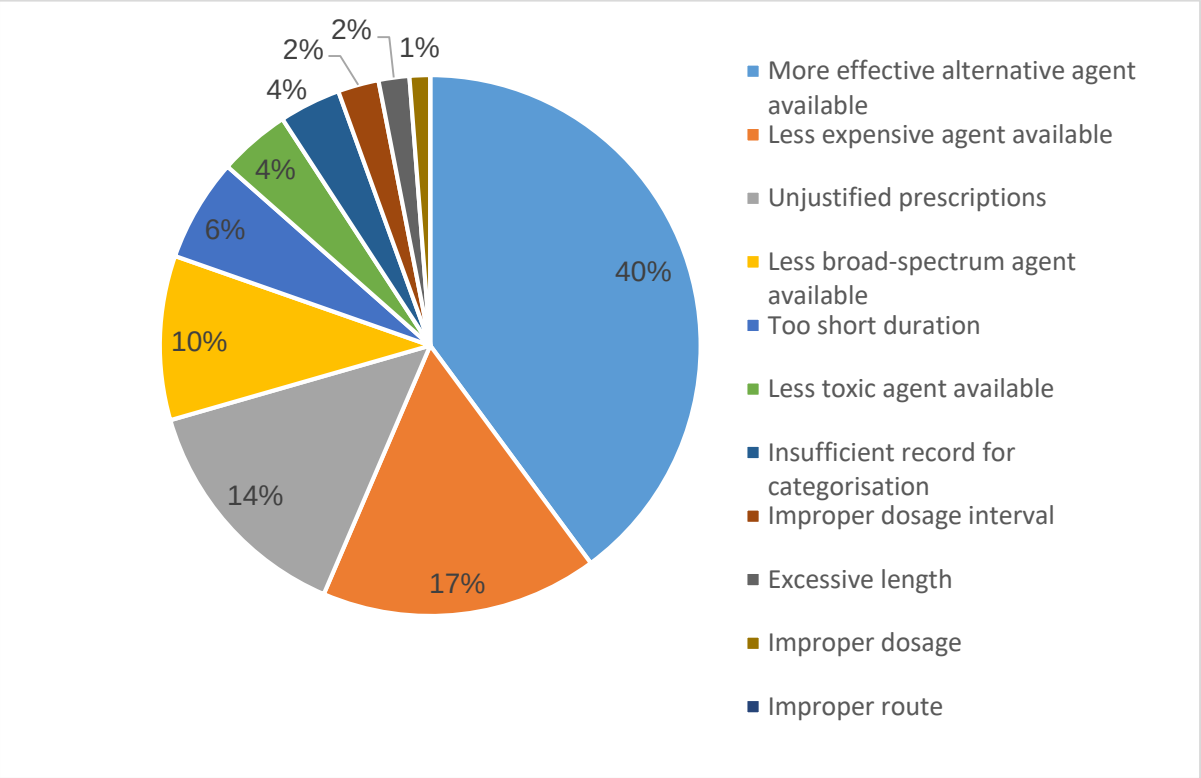

Figure 4.16: Categories of inappropriate antibiotic utilisation in the intervention stage.

4.4.3 Appropriateness of all prophylactic therapy

In the baseline stage of the study, 64% of all prophylactic therapy including surgical prophylaxis and cases where fluconazole was used prophylactically (Figure 4.17). The latter was used in patients with suspected intra-abdominal sepsis, while in the intervention stage 59% of prophylactic therapy was inappropriate (Figure 4.18).

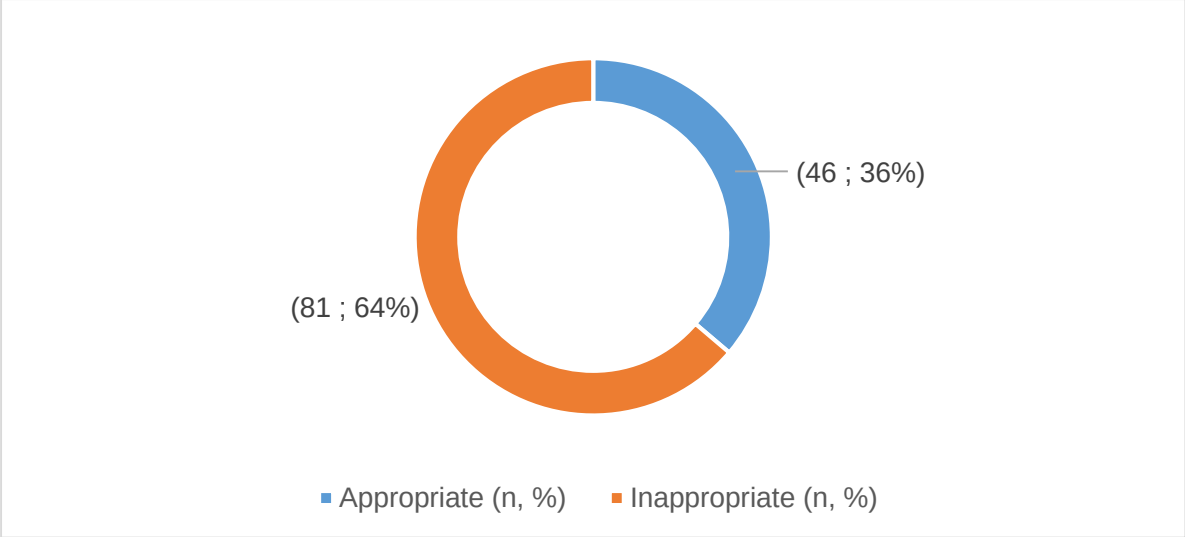

Figure 4.17: Appropriateness of prescriptions used for all prophylactic therapy in the baseline stage.

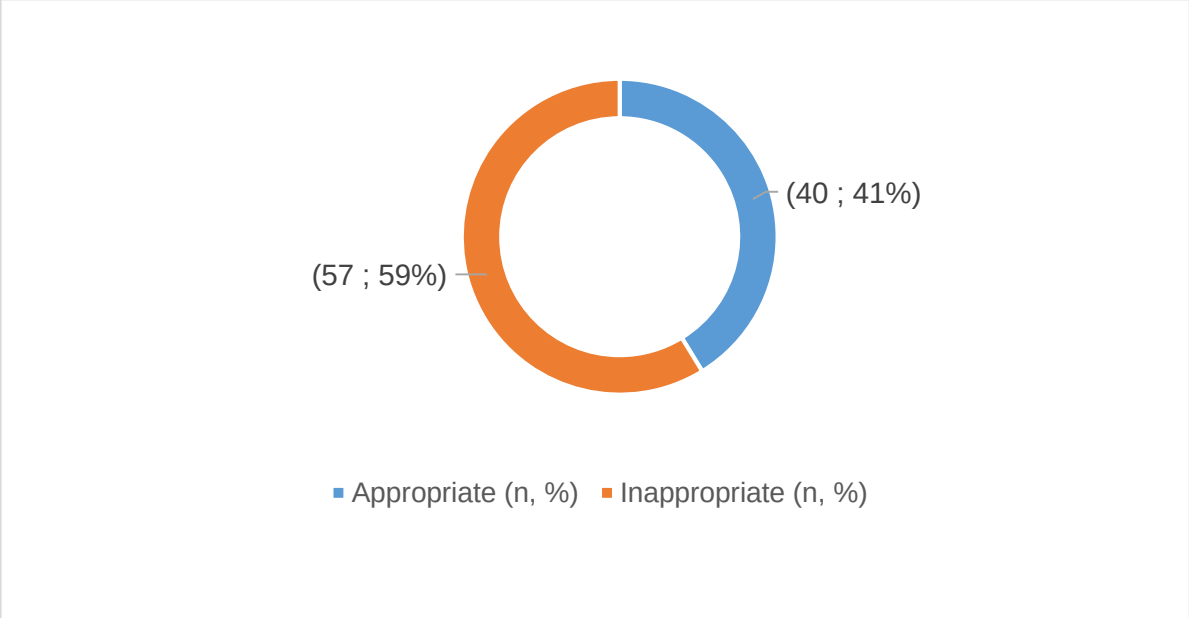

Figure 4.18: Appropriateness of prescriptions used for all prophylactic therapy in the intervention stage.

4.4.4 Appropriateness of surgical prophylaxis

Amoxicillin/clavulanic acid was the most commonly used agent for surgical prophylaxis 68.03% in the baseline stage followed by cefazolin at 29.51% (Table 4.27). According to the classification system used and based on the South African guidelines, nearly 65% of all surgical prophylaxis was inappropriate based on the agent choice, while (n = 9/122) 7.34% was inappropriate based on the duration of prophylaxis. Similarly, in the intervention stage amoxicillin/clavulanic acid and cefazolin were the two most frequently used agents for surgical prophylaxis, and 61.54% of all surgical prophylaxis in this stage was inappropriate based on the choice of agent (Table 4.28), while 6.59% (n = 6/91) was inappropriate based on the duration of prophylaxis.

Table 4.27: Surgical prophylaxis in the baseline stage.

Agents Used for Surgical Prophylaxis	**Vascular Ward n (%)**	**General Ward n (%)**	**Total of both Wards n (%)**
Amoxicillin/Clavulanic acid	18 (60.00)	65 (70.65)	83 (68.03)
Cefazolin	11(36.67)	25 (27.17)	36 (29.51)
Clindamycin	1 (3.33)	1 (1.09)	2 (1.64)
Metronidazole	0 (0.00)	1 (1.09)	1 (0.82)
Total	30 (100.00)	92 (100.00)	122 (100.00)
Appropriateness of Surgical Prophylaxis			
Inappropriate	17 (56.67)	62 (67.39)	79 (64.75)
Appropriate	13 (43.34)	30 (32.61)0	43 (35.25)
Total	**30 (100.00)**	**92 (100.00)**	**122 (100.00)**

Table 4.28: Surgical prophylaxis in the intervention stage.

Agents Used for Surgical Prophylaxis	**Vascular Ward n (%)**	**General Ward n (%)**	**Total of both Wards n (%)**
Amoxicillin/Clavulanic acid	18 (50.00)	38 (69.09)	56 (61.54)
Cefazolin	17 (47.22)	14 (25.45)	31 (34.07)
Clindamycin	0 (0.00)	3 (5.45)	3 (3.30)
Metronidazole	1 (2.78)	0 (0.00)	1 (1.10)
Total	36 (100.00)	55 (100.00)	91 (100.00)
Appropriateness of Surgical Prophylaxis			
Inappropriate	19 (52.78)	37 (67.27)	56 (61.54)
Appropriate	17 (4.22)	18 (32.73)	35 (38.46)
Total	**36 (100.00)**	**55 (100.00)**	**91 (100.00)**

4.4.5 Appropriateness of empiric/targeted therapy

Up to 21% of all antibiotic prescriptions used for empiric and targeted indications in the baseline were measured as inappropriate based on the Gyssen's classification (Figure 4.19) (Appendix 4); while in the intervention stage 18% of antibiotics utilised for empiric and targeted treatment were inappropriate (Figure 4.20).

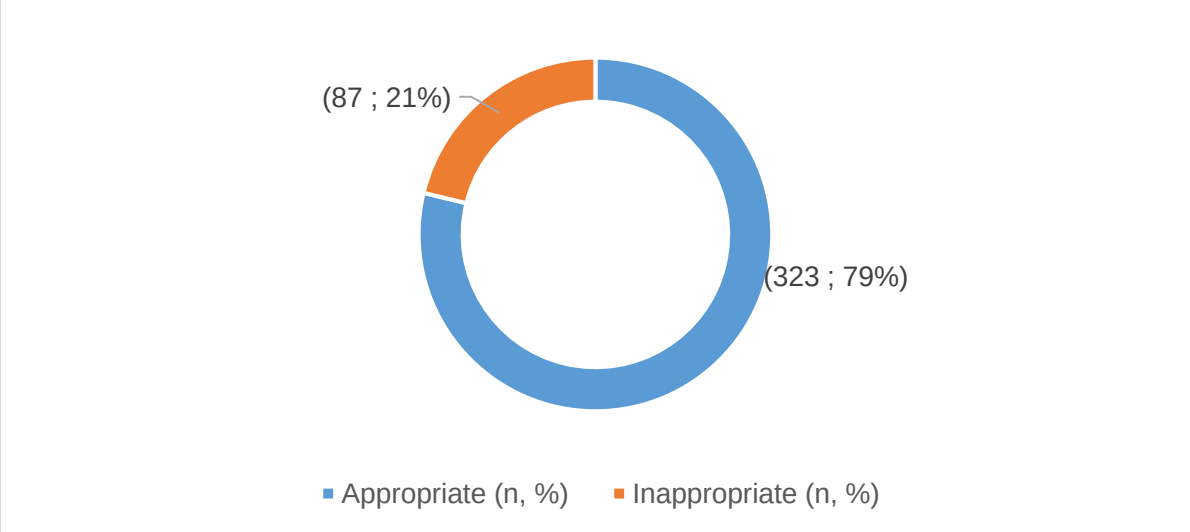

Figure 4.19: Appropriateness of prescriptions for empiric and targeted therapy in the baseline stage.

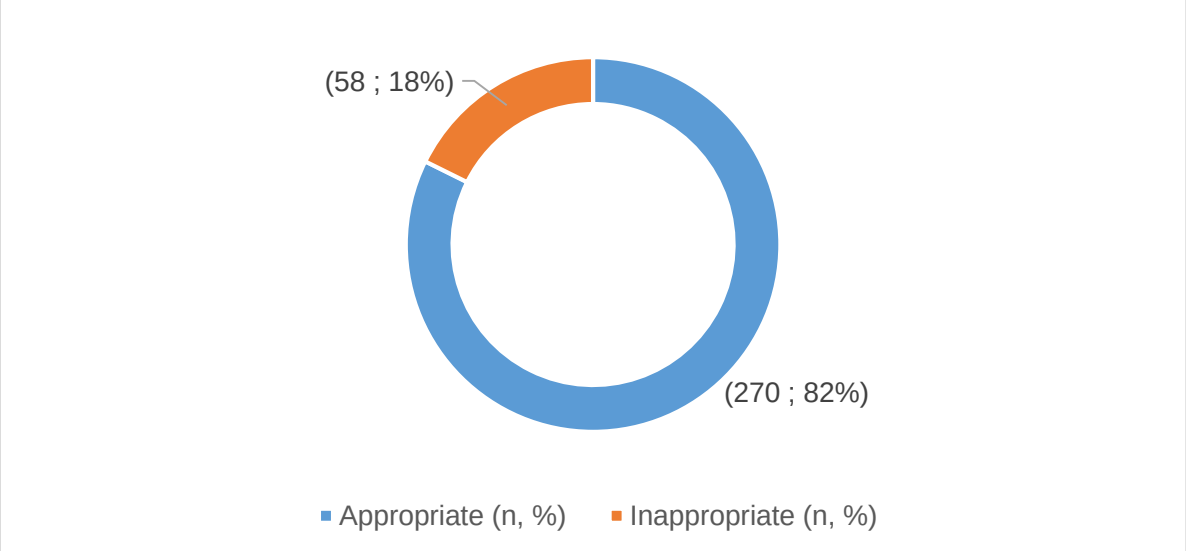

Figure 4.20: Appropriateness of prescriptions for empiric and targeted therapy in the intervention stage.

4.4.6 Predictors of appropriateness of antibiotic prescription

The association between the dependent and independent variables for appropriateness of antibiotics prescription are shown in Table 4.29 using univariate and multivariate logistic regression models. In the unadjusted model, the age of patients was significantly associated with the appropriateness of antibiotics prescription. Patients aged 36 to 75 years were 47% more likely to have an appropriate antibiotics prescription compared to those aged 18 to 35 years and this was statistically significant, (OR: 1.47, 95%CI: 1.01 - 2.14). For patients aged 75 years and above, they were 2.32 times more likely to have an appropriate prescription of antibiotics compared to those aged 18 to 35 years; however, this was not statistically significant (OR: 2.32, 95% CI: 0.96 - 5.63). After adjusting for DoTh, type of surgery, whether microscopy or culture was requested, type of diagnoses and type of ward, there was an increasing odds of appropriateness with increasing age of patients such that patients aged 36 to 75 years were 44% more likely to have appropriate prescription of antibiotics compared those aged 18 to 35 years old (OR: 1.44, 95%CI: 0.95 - 2.19). Patients aged >75 years were 3.09 times more likely to have appropriate antibiotics prescription compared to those aged 18 to 35 years and this was statistically significant (OR: 3.09, 95% CI: 1.11 - 8.14).

The DoTh by patients is associated with appropriateness in the crude model such that patients who had antibiotics for 2 to 7 days were 3.21 times more likely to have an appropriate prescription of antibiotics compared to those who had treatment for >7 days and this was statistically significant (OR: 3.21, 95%CI: 1.63 - 5.23). After adjusting for patient's age, type of surgery, whether microscopy or culture tests was requested, type of diagnoses, and type of ward, patients who were treated for 2 to 7 days were 64% more likely to have an appropriate prescription of antibiotics compared to those who received them for >7 days, and this was statistically significant (OR: 1.64, 95%CI: 1.06 - 3.41).

There was a statistically significant association between the type of surgery and appropriateness of antibiotics prescription (p = 0.001). In the crude model, there were increased odds of 35% and 80% of appropriate prescription of antibiotics for patients who had clean and contaminated surgery, respectively, compared

to those who had clean-contaminated surgery - but this was not statistically significant (OR: 1.35, 95%CI: 0.74 - 2.46; OR: 1.80, 95%CI: 0.98 - 3.29).

Table 4.29: Crude and adjusted odds ratio (OR) of the appropriateness of antibiotics prescription, where the correct classification rate of the model is 71.23% (ǂ: Statistically Significant).

Characteristics	Crude		Adjusted*	
	OR (95% CI)	P-Value	OR (95% CI)	P-Value
Age Group (in Years)				
18 - 35	1.00		1.00	
36 - 75	1.47 (1.01 - 2.14)	0.044ǂ	1.44 (0.95 - 2.19)	0.084
>75	2.32 (0.96 - 5.63)	0.063	3.09 (1.11 - 8.14)	0.030ǂ
DoTh (in days)				
>7	1.00		1.00	
2 – 7	3.21 (1.63 - 5.23)	<0.001 ǂ	1.64 (1.06 - 3.41)	0.028 ǂ
Type of Surgery				
Clean-contaminated surgery	1.00		1.00	
Clean surgery	1.35 (0.74 - 2.46)	0.331	1.52 (0.77 - 3.01)	0.223
Contaminated surgery	1.80 (0.98 - 3.29)	0.058	3.11 (1.49 - 6.48)	0.002ǂ
Dirty surgery	3.31 (1.82 - 5.99)	<0.001 ǂ	2.34 (1.15 - 4.76)	0.019 ǂ
No surgical procedure done	3.16 (1.57 - 6.52)	0.002 ǂ	3.93 (1.77 -8.73)	0.001ǂ
Whether Culture/Microscopy was Requested				
Culture/microscopy requested	1.00		1.00	
No culture/microscopy requested	0.51 (0.35 - 0.74)	<0.001 ǂ	0.69 (0.44 - 1.10)	0.210
Type of Diagnoses				
Gallbladder, biliary tract and Liver cases	1.00		1.00	
Lower GI cases	1.03 (0.44 - 2.41)	0.943	0.52 (0.19 - 1.40)	0.197
Other general surgery cases	1.15 (0.48 - 2.72)	0.758	0.52 (0.18 - 1.40)	0.217
Pancreas, spleen and appendix cases	3.90 (1.59 - 9.55)	0.003 ǂ	2.01 (0.71 - 5.67)	0.186
Upper GI cases	0.82 (0.33 - 2.01)	0.659	0.56 (0.20 - 1.62)	0.286
Vascular cases	1.70 (0.71 - 4.05)	0.234	0.95 (0.23 - 3.88)	0.940
Type of Ward				
Vascular Ward	1.00		1.00	
General Surgery ward	0.88 (1.58 - 3.51)	<0.001 ǂ	1.33 (0.49 - 3.58)	0.578
Gram-Positive/-Negative Bacteria and Fungi				
Fungi	1.00			
Gram-negative bacteria	1.13 (0.20 - 6.53)	0.889		
Gram-positive bacteria	0.95 (0.16 - 5.63)	0.959		

Patients who had dirty surgery and those who had no surgical procedure are 3.31 and 3.26 times more likely to have an appropriate prescription of antibiotics, respectively; compared to those who had clean-contaminated surgery (OR: 3.31, 95%CI: 1.82 - 5.99; OR: 3.16, 95%CI: 1.57 - 6.52). After adjusting for other variables, there was an increased odds of 52% for patients who had clean surgery to have an appropriate antibiotic prescription compared to patients who had clean-contaminated surgery (OR: 1.52, 95%CI: 0.77-3.01). Patients who had contaminated surgery, dirty surgery, and no surgical procedure had statistically significant odds of 3.11, 2.34 and 3.93, respectively; compared to those who had clean-contaminated surgery (OR: 3.11, 95%CI: 1.49 - 6.48, OR: 2.34; 95%CI: 1.15 - 4.76, OR: 3.93, 95%CI: 1.77 - 8.73).

There were 51% reduced odds of appropriate prescription of antibiotics for patients who had no culture/microscopy requested compared to those with culture/microscopy requested. This was statistically significant (OR: 0.51, 95%CI: 0.35 - 0.74). There were increased odds of 3%, 15%, and 70% of receiving an appropriate prescription in lower GI cases, other general surgical cases, and vascular cases, respectively; compared to those with gallbladder, biliary tract and liver cases. This were also not statistically significant (OR: 1.03, 95%CI: 0.44 - 2.41; OR: 1.15, 95%CI: 0.48 - 2.72; OR: 1.70, 95%CI: 0.71 - 4.05). Patients who were diagnosed with pancreas, spleen and appendix cases were 3.9 times more likely to have an appropriate prescription of antibiotics compared to those diagnosed of the gallbladder, biliary tract and liver cases. This was statistically significant (OR: 3.90, 95%CI: 1.59 - 9.55). There was an 82% reduction in the odds of appropriate prescription of antibiotics for patients diagnosed with upper GI cases compared to those diagnosed with gallbladder, biliary tract and liver cases. This was not statistically significant. (OR: 0.82, 95%CI: 0.33 - 2.01). After adjusting for other variables there was a reduction in the odds of appropriate prescriptions for patients diagnosed with lower GI cases, other general surgical cases, upper GI cases and vascular case compared to those with diagnoses of gallbladder, biliary tract and liver cases. This was not statistically significant (OR: 0.52, 95%CI: 0.19 - 1.40; OR: 0.52. 95%CI: 0.18 - 1.40; OR: 0.56, 95%CI: 0.20 - 1.62, OR: 0.95, 95%CI: 0.23 - 3.88).

In the unadjusted model, the type of ward was significantly associated with the appropriateness of antibiotics prescription (OR: 0.88, 95%CI: 1.58 - 3.51), such that patients admitted in the General Surgery Ward were 88% less likely to have an appropriate prescription of antibiotics compared to those admitted to the Vascular Ward. Although there was a 33% increased odds of appropriate antibiotics prescriptions for patients admitted to the General Ward compared to those in the Vascular Ward, after adjusting for other variables i.e. Age, DoTh, type of surgery, whether microscopy or culture was requested, type of diagnoses and type of ward in the model, the statistical significance observed in the crude model disappeared (OR: 1.33, 95% CI: 0.49 - 3.58). While there were increased odds of 13% and 95% of appropriate prescription of antibiotics for Gram-negative and Gram-positive bacteria, respectively; compared with fungi, this is not statistically significant. (OR: 1.13, 95% CI: 0.20 - 6.53, OR: 1.33, 95%CI: 0.19 - 9.27).

4.5 COMPLIANCE RATE TO AMS RECOMMENDATIONS

About 71.18% of the recommendations made during the AMS round were implemented, however there were some recommendations that were not found in patient records after discharge (Table 4.30).

Table 4.30: Rate of recommendations compliance.

Recommendations	**Number of Recommendations**	**Compliance Rate**
Intravenous to oral route	68	53
Oral to intravenous route	13	9
Discontinuation of an antibiotic therapy	54	36
Removal of intravenous cannulae	16	16
Removal of urethral catheters	4	4
Tissue cultures	67	43
CRP	144	103
Procalcitonin	41	32
Blood cultures	52	41
Other specimen cultures	27	15
Conversion from broad-spectrum to narrow-spectrum antibiotics	38	21
Total	**524**	**373**

4.6 COST

4.6.1 Average cost of antibiotics and laboratory investigations

The average cost of antibiotics per patient in the Vascular Ward was R 268.23 ± 389.32 in the baseline stage (Table 4.31); while in the intervention stage, it reduced to R 228.03 ± 326.88 (Table 4.32). However, in the General Ward, the average cost of antibiotic per patient was less at R 219.80 ± 400.75 in the baseline stage compared to R 284.06 ± 461.28 in the intervention stage. Overall, the average costs of antibiotics per patient in the baseline and intervention were R 231.06 ± 398.21 and R 265.81 ± 422.66, respectively; which showed an increase of R 34.75 per patient in the intervention stage. The average costs of CRP and FBC per patient in the baseline stage were R 304 ± 447.51 and R 187.51 ± 273.00, respectively; while in the intervention stage these costs increased to R 452.82 ± 400.98 and R 285.22 ± 258.03, respectively. The mean cost of PCT per patient in the Vascular Wards during the baseline stage was R 641.42 ± 594.81 and this increased to R 839.95 ± 666.90 in the intervention stage in the same ward. There was also an increase in the cost of MCS per patient in the intervention stage. However, this increase in the cost was not due to an increase in the cost of the test, rather due to an increase in the number of tests ordered (Tables 4.31 and 4.32).

Table 4.31: Patient's average cost of antibiotics and laboratory investigations in the baseline stage

Characteristics	**Vascular Ward Mean (R)**	**General Surgical Ward Mean (R)**	**Total of both Wards Mean (R)**
Average cost of antibiotic per patient	268.23 ± 389.32	219.80 ± 400.75	231.06 ± 398.21
Average cost of PCT per patient	641.42 5 ± 94.81	1259.93 ± 3334.51	1040.45 ± 2705.48
Average cost of CRP per patient	434.84 3 ± 67.29	274.44 ± 459.58	304.00 ± 447.51
Average cost of FBC per patient	265.13 ± 199.59	169.14 ± 284.96	187.51± 273.00
Average cost of MCS per patient	96.33 ± 42.52	102.42 ± 54.42	101.41 ± 52.63

Table 4.32: Patient's average cost of antibiotics and laboratory investigations in the intervention stage.

Characteristics	Vascular Ward Mean (R)	General Surgical Ward Mean (R)	Total of both Wards Mean (R)
Average cost of antibiotic per patient	228.03 ± 326.88	284.06 ± 61.28	265.81± 422.66
Average cost of PCT per patient	839.95 ± 666.90	1124.80 ± 1122.66	1021.94 ± 987.12
Average cost of CRP per patient	446.65 ± 414.82	455.32 ± 396.78	452.82 ± 400.98
Average cost of FBC per patient	279.12 ± 280.62	287.89 ± 248.53	285.22 ± 258.03
Average cost of MCS per patient	104.35 ± 61.61	132.71 ± 84.12	117.81 ± 71.64

4.6.2 **Overall antibiotic cost**

Amoxicillin/clavulanic acid was the highest prescribed agent in both stages of the study followed by piperacillin/tazobactam, but in term of cost incurred piperacillin/tazobactam was the highest (Tables 4.33 and 4.34). The frequency of amoxicillin/clavulanic acid prescription in the baseline and intervention stages were 52.59% and 33.71%, respectively. An independent sample *t*-test showed that there was no statistically significant difference in the overall cost of antibiotics in the baseline and the intervention $p = 0.21$.

Table 4.33: Cost of antibiotics utilisation in the baseline stage.

Name of Antibiotics	Number of Prescriptions	(%) of Total prescriptions	Total Cost per Antibiotic (R) (95% CI)
Amoxicillin/ Clavulanic acid	233	52.59	22,990.19 (19,797.05 - 26,183.33)
Piperacillin/ Tazobactam	72	16.26	47,726.98 (38,340.64 - 57,133.32)
Cefazolin	36	8.13	434.18 (366.84 - 501.51)
Metronidazole	20	4.52	697.87 (210.56 - 1,185.17)
Fluconazole	13	2.93	2,677.43 (995.99 - 4,358.87)
Vancomycin	10	2.26	1,721.93 (233.05 - 3,210.81)
Cloxacillin	8	1.81	1,839.92 (982.61 - 2,678.27)
Imipenem	7	1.58	10,112.00 (4799.70 - 15,424.30)
Ciprofloxacin	6	1.35	751.10 (-150.79 - 1,652.99)
Sulfamethoxazole/ Trimethoprim	5	1.13	9.87 (3.37 - 16.38)
Clarithromycin	5	1.13	1,256.74 (785.82 - 1,727.65)
Cefepime	4	0.90	2,857.47 (757.05 - 4,957.90)
Amoxicillin	4	0.90	10.52 (3.89 - 17.14)
Azithromycin	3	0.67	1,768.70 (655.84 - 2,881.56)
Clindamycin	3	0.68	66.36 (29.10 - 103.62)
Colistin	3	0.67	2,031.48 (942.60 - 3,120.36)
Amikacin	2	0.45	1,134.56 (-776.70 - 3,045.82)
Ertapenem	2	0.45	1,504.99 (119.44 - 2,890.54)
Erythromycin	2	0.45	1,504.99 (119.44 - 2,890.54)
Gentamycin	2	0.45	144.87 (15.45 - 274.29)
Amphotericin B	1	0.23	565.50
Ceftazidime	1	0.23	395.39
Ceftriaxone	1	0.23	11.68
Total	443	100.00	

Table 4.34: Cost of antibiotics utilisation in the intervention stage.

Name of Antibiotics	Number of Prescriptions	(%) of Total Prescription	Total Cost per Antibiotic (R) (95% CI)
Amoxicillin/ Clavulanic acid	149	33.71	12,224.55 (9,950.03 -14,417.83)
Piperacillin/ Tazobactam	115	26.02	55,501.51 (49,626.34 - 61,376.68)
Cefazolin	31	7.01	769.11 (434.77- 1,103.46)
Fluconazole	19	4.30	2,000.41 (949.63 - 3,051.18)
Ertapenem	18	4.07	27,256.42 (1,9815.83 - 3,4697.01)
Metronidazole	18	4.07	415.64 (34.29 - 796.98)
Azithromycin	15	3.39	3,188.39 (2,025.08 - 4,351.70)
Ciprofloxacin	13	2.94	1,243.14 (423.86 - 2,062.42)
Clindamycin	12	2.71	1,412.52 (647.63 - 2,177.41)
Imipenem	8	1.81	3,258.75 (1,911.65 - 4,605.85)
Clarithromycin	7	1.58	217.89 (89.39 - 346.40)
Vancomycin	6	1.36	1,621.82 (95.24 - 3,148.40)
Amoxicillin	5	1.13	8.92 (3.58 - 14.25)
Cefepime	3	0.68	2,650.91 (752.75 - 4,549.07)
Cefotaxime	3	0.68	306.26 (274.58 - 337.94)
Cloxacillin	3	0.68	997.18 (103.54 - 1,890.82)
Nystatin	3	0.68	6.82 (2.35 - 11.29)
Sulfamethoxazole/ Trimethoprim	3	0.68	4.56 (3.52 - 5.59)
Amikacin	2	0.45	162.08 (2.81 - 321.35)
Erythromycin	2	0.45	375.00 (227.60 - 522.40)
Meropenem	2	0.45	438.90 (-177.24 - 1,055.04)
Ceftazidime	1	0.23	428.34
Ceftriaxone	1	0.23	40.87
Doxycycline	1	0.23	4.10
Gentamycin	1	0.23	32.93
Linezolid	1	0.23	2,920.30
Total	442	100.00	

CHAPTER FIVE: DISCUSSIONS AND CONCLUSION

5.1 INTRODUCTION

Over-consumption and inappropriate utilisation of antibiotics are the main factors fuelling AMR with consequent additional hospital costs. AMS programmes are the gold standard in improving appropriate antibiotic utilisation, with a reduction of antibiotic consumption and cost in a hospital setting (Akhloufi *et al.*, 2015; Klepser *et al.*, 2016; Sartelli *et al.*, 2016a). However, there are a limited number of intervention studies conducted in Africa, especially in a surgical setting, designed to encourage appropriate antibiotic utilisation. Hence the need to conduct this study. This study aimed at investigating the appropriateness of antibiotic consumption and the impact of introducing an AMS intervention. It involved a retrospective review of patient records in the baseline stage followed by an intervention which involved a weekly antibiotic ward round led by an infectious diseases specialist. A recent study of the impact of implementation of an AMS programme which involved a weekly antibiotic round in the medical department of a South African public tertiary hospital showed a considerable reduction of consumption and cost of antibiotics (Boyles *et al.*, 2017).

SSIs constitute a significant proportion of hospital-acquired infections (Anderson *et al.*, 2013) which increase the duration of hospital stay and cost (Anderson *et al.*, 2013; Călina *et al.*, 2017). Surgical infections are associated with high morbidity / mortality, poor clinical outcomes and treatment failures if appropriate antibiotic therapies are not instituted. A key component in the management of these infections is good source control and appropriate antibiotic management (Sartelli *et al.*, 2016a). Antibiotics play a critical role in the management of surgical conditions, cancer therapy and organ transplant. However, irrational usage of antibiotics is associated with the selection and spread of resistant pathogens (Bell, 2014). Berrington (2010) reported that the measurement of antibiotic consumption is a principal component of any AMS programme to enable comparison and benchmarking between study stages and other studies.

5.2 PATIENT DEMOGRAPHIC CHARACTERISTICS

The demographic characteristics of the participants in both stages of the study show that the patients were relatively evenly distributed between males and females with a slightly higher proportion of males in the study. More patients were admitted into the General Ward compared to the Vascular Ward which is likely because patients stayed longer in the Vascular Ward (Tables 4.1 and 4.2). Other studies of antibiotic utilisation in surgical settings in other parts of the world also show a higher preponderance of males (James and Venu, 2016; Zygourakis *et al.*, 2017) where a study in an Australian hospital involving different departments including surgery showed a preponderance of males (58%) (Akhloufi *et al.,* 2015) similar to the 66.6% of males noted in an Indian ICU (Anand *et al.*, 2016).

The overall mean age of the patients was 45.77 ± 16.81 and 51.50 ± 15.91 years in the baseline and intervention stages, respectively (Section 4.1.2). The statistically significant difference in age between the study stages, showed that older patients were admitted during the intervention stage. This could have been that the patients in the intervention stage could have had more co-morbidities and ICU admissions compared with their counterparts in the baseline stage due to their advanced age. Most of the patients in both stages of the study fell within the age category of 36 to 75 years. In a similar study conducted in an Indian ICU, most patients were within the 51 to 65-year-age bracket with a mean age of 52.9 ± 16.9 years (Anand *et al.,* 2016). Other studies in general wards have reported average ages of 54.8 ± 13.2 years (James and Venu, 2016) and 60 years (Ingram *et al.*, 2012).

The overall average LOS of patients in the baseline and intervention stages were 8.27 ± 9.52 and 13.23 ± 11.81 days, respectively (Section 4.1.3). There was also a statistically significant difference in the overall LOS between the two stages of the study. Although many AMS programmes have reported a reduction in LOS during the intervention stage (Nault *et al.*, 2016; Sintchenko *et al.*, 2005), in contrast, this study showed an increase in LOS. This may be due to the fact this study was conducted in a surgical setting and older patients were admitted during the intervention stage, compared to the baseline stage. Differences in LOS were observed between the wards; where patients in the

Vascular Ward stayed longer in both stages compared with those in the General Ward, probably due to their advanced age. The average LOS was 12.66 ± 10.03 days in the Vascular Ward and 7.16 ± 9.08 days in the General Ward at baseline stage; compared to 16.94 ± 15.44 in the Vascular Ward and 11.55 ± 9.32 days in the General Ward during the intervention stage (Section 4.1.3). It was observed in this study that patients with peripheral vascular disease with ischemia and other vascular complications of diabetes stayed longer, not because of infections, but because they had a series of procedures such as angiograms, angioplasties and bypass surgeries in attempting limb salvage before resorting to amputation when all conservative measures failed. It has been observed that many patients stayed longer because they were on IV therapy although they do not need IV medications. So early IV to oral conversion alone is shown to reduce the LOS in many AMS studies (Barlam *et al.,* 2016; Shrayteh *et al.*, 2014), and one may expect a reduction in the LOS with reduction in the use of IV antibiotics.

It was also noted that patients had a long waiting time before surgical operations especially in the Vascular Ward. Although, due to their advanced age in the intervention stage, patients stood a higher chance of having other associated co-morbidities which may have extended their hospital stay. James and Venu (2016) found the LOS to be 16.6 ± 8.1 days in a gastroenterology unit of a tertiary hospital in India; this being higher than the LOS of the patients in the General Ward of this study which comprised of a large proportion of gastroenterology cases. Patients who underwent vascular neurosurgical procedures in the USA had an average LOS of 11.2 to 13.9 days (Zygourakis *et al.*, 2017). This was nearly the same as the LOS of the patients in the Vascular Ward in the baseline stage; but was slightly lower than the LOS of patient in the intervention stage. An AMS programme in a surgical setting at a Taiwanese hospital did not find any significant difference in the average LOS between the study stages; where the average LOS was 6.2 ± 7.0 and 6.3 ± 7.4 days in the pre-implementation and implementation stages, respectively (Chang *et al.*, 2006). Similarly, a three-year AMS programme at another Taiwanese teaching hospital did not find any significant difference in LOS (Lin *et al.*, 2013). Recently, an AMS study in Cape Town conducted in a medical setting showed an initial reduction in mean LOS from 7.4 days in 2011 to 6.5 days in 2013; but

subsequently increased to 7.6 days in 2015, with no reason given for this increase (Boyles *et al.*, 2017).

Clean and dirty surgical operations were the most common surgical operations performed on patients in the Vascular Ward during baseline stage, whereas in the General Ward contaminated surgical operations were the most frequent, followed by clean procedures (Figure 4.5). During the intervention stage, the dirty and clean operations were still the most common operations in the Vascular Ward with a preponderance of dirty procedures and this was likely because of increased cases of patients who had amputations during this stage (Figure 4.6). While in the General Ward clean operations were the most common surgical operations followed by contaminated procedures (Figure 4.6). Patients who had dirty procedures were likely to stay longer and consume more antibiotics, while those with clean surgeries were likely to consume less. However, prompt and early source control may reduce LOS and volume of antibiotic consumption (Sartelli *et al.*, 2016a). A 3.5-year study in a gastrointestinal unit at a Dutch tertiary health centre observed slightly different trends to our General Ward, in which 12% of surgeries were clean cases, 42% clean-contaminated, 25% contaminated and 20% dirty (Ramcharan *et al.*, 2014). Most patients in both stages of the study had only one procedure, however, the proportion of those who had two and more procedures were higher in the intervention stage (Tables 4.3 and 4.4).

In this study, as there was a significant increase in the age and LOS during the intervention stage, ordinarily one should expect an increased consumption of antibiotics. However, with the intervention which encouraged source control, rational antibiotic utilisation and unnecessary antibiotic consumption in patients who were waiting for surgical procedures or even after surgical operations this led to a reduction in antibiotic consumption during intervention stage (Tables 4.13 and 4.14).

5.3 ANTIBIOTIC UTILISATION

The five most commonly prescribed agents in the baseline stage were amoxicillin/clavulanic acid, piperacillin/tazobactam, cefazolin, metronidazole and fluconazole (Table 4.15). During the intervention, amoxicillin/clavulanic

acid, piperacillin/tazobactam, cefazolin, fluconazole, ertapenem and metronidazole were the most frequently used antibiotics (Table 4.16). There was an increase in the utilisation of piperacillin/tazobactam in the intervention stage which is likely due to an increase in the prevalence of *P. aeruginosa* compared to the baseline stage (Table 4.20). On the other hand, there was also an increase in the consumption of ertapenem in the intervention stage, although it was mostly used for culture directed therapy and this was mostly due to an increase in the prevalence of multidrug-resistant *Klebsiella pneumoniae* during the intervention stage (Table 4.22). Ertapenem has shown in vitro activity against ESBL- producing *Enterobacteriaceae* such as *K. pneumoniae* (Livermore *et al.*, 2003). A case of an ertapenem – resistant ESBL producing *K. pneumoniae* has since been reported in South Africa (Elliott *et al.*, 2006). More recently *Klebsiella pneumoniae* carbapenemase which are plasmid-encoded enzymes capable of hydrolysing all β- lactams including monobactams, extended-spectrum cephalosporins and carbapenems have been reported in South Africa (Vasaikar *et al.*, 2017). South African studies have looked at the utilisation of antibiotics, but only a few have specified the type of antibiotic used for treating infections. A recent study, in Cape Town in a medical setting found ampicillin and benzylpenicillin as the most frequently prescribed agents followed by ceftriaxone, cloxacillin and carbapenems; while amoxicillin/clavulanic acid was among the least prescribed agents (Boyles *et al.*, 2017). Though the types of bacterial infections treated were not mentioned in the Cape Town study to justify the choice of the antibiotics, the difference in the choice of antibiotics observed with the current study was probably because the two studies were conducted in different settings, with likely differences in prevalence of pathogens.

In a study conducted at a Dutch tertiary centre, β-lactam - β-lactamase inhibitors combination – amoxicillin/clavulanic acid 34%, and piperacillin/tazobactam 26% were the most frequently used antibacterials followed by fluoroquinolones 37%. Where 17.3% of all prescriptions were ordered in surgery wards (Akhloufi *et al.*, 2015). Although, the types of bacterial infections treated and reasons for the choice of these antibiotics were not reported in the Dutch study, the choice of antibiotics were similar to the current study. Researchers in an Indian ICU found

ceftriaxone 22.77% as the most commonly utilised agent, followed by piperacillin/tazobactam 15.79%, metronidazole 12.03%, amoxicillin/clavulanic acid 6.44%, and azithromycin 4.34% (Anand *et al.*, 2016). In Europe, an AMS programme showed cefuroxime as the most frequently prescribed agent in both control and post-intervention stages of the study in a Hungarian Surgical ICU, followed by vancomycin and ciprofloxacin in the control stage, while amoxicillin/clavulanic acid and meropenem in the post-intervention stage. Where MRSA, VRE, *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* were the most prevalent bacteria in both stages of the study (Peto *et al.*, 2008).

Most of the patients in both stages of this study had one antibiotic, followed by those who had two and three agents, while few even had four and more during their inpatient stay (Figure 4.7 and 4.8). This is similar to the Akhloufi study where 68.3% of patients had only one antibiotic, 25.8% had two agents and 5.9% received three and more agents (Akhloufi *et al.*, 2015). In this study, most of the antibiotic therapies were empiric in nature, macrolides such as erythromycin were used in newly operated patients as a prokinetic agent, while azithromycin as an anti-biofilm agent (Figures 4.9 and 4.10). There was a shift from empiric to culture targeted therapy between baseline and intervention stages with 31.34% more scripts based on the laboratory results, although the shift was statistically insignificant ($p = 0.125$) (Figures 4.9 and 4.10). Results of a similar study at a secondary Spanish Health Centre from 2009 to 2011 showed a reduction of empiric antibiotics therapy from 46% in 2009 to 31% in 2011 due to the implementation of an AMS programme (Del Arco *et al.*, 2015). The percentage of inappropriate antibiotic utilisation in another Spanish Hospital in the first quarter of their AMS programme was 56% of surgical prophylaxis, 55.2% of empiric therapy and 46.6% of targeted therapy. However, this reduced to 15.8% of surgical prophylaxis, 33.3% empiric and 21.6% of targeted therapy in the fourth quarter of the program (Cisneros *et al.*, 2014). These studies have indicated an improvement in the utilisation of antibiotics.

More patients received combination therapy during the intervention stage (Section 4.2.6). This was mostly an appropriate combination used to treat infections caused by multi-drug resistant *Klebsiella pneumoniae* and

Acinetobacter baumannii. The reported prevalence of these pathogens increased in the intervention stage (Tables 4.21 and 4.22), probably due to increases in the request of cultures during AMS rounds. Also, de-escalation to narrow-spectrum antibiotics from broader agents initiated by the surgeons during AMS rounds based on the results of cultures could have also increased the number of antibiotics received by the patients in this stage. Of note, in the intervention stage most of the patients that received more than one antibiotic had them sequentially, except in situations where there was need to broaden the empiric cover.

5.3.1 Antibiotic consumption

There was a statistically significant reduction in the consumption of antibiotics between the two stages of the study, from 739.30 DDDs/1000 patient days, in the baseline to 564.93 DDDs/1000 patient days in the intervention stage (p = 0.038) (Tables 4.13 and 4.14). This concurred with many AMS studies, such as the one conducted at two medical wards of Groote Schuur Academic Hospital in Cape Town where there was a reported 19.6% reduction in antibiotic consumption from 592.0 DDDs/1000 patient days in the pre-implementation stage to 475.8 DDDs/1000 patient days in the implementation stage after introduction of dedicated antibiotic chart and weekly antibiotic round (Boyles *et al.*, 2013). Recently Boyles reported a sustained reduction in antibiotic utilisation from 1,046 DDDs/1000 patient bed days in 2011 to 864 DDDs/1000 patient beds in 2015 after extending the programme to two other medical wards (Boyles *et al.*, 2017). Although our intervention resulted in a significant reduction of antibiotic consumption, it is still high compared to what was found in the 2013 Cape Town study where the study took place in medical wards compared to the surgical setting in this study (Tables 4.13 and 4.14). Other AMS studies showed a reduction in the consumption of antibiotic during second stage, except in a study at surgical/medical ICU of an academic hospital in Toronto where an increased consumption was reported (Table 5.1).

In both stages of the study the average daily doses of the most frequently used drugs such as IV amoxicillin/clavulanic acid and piperacillin/tazobactam used for treatment purposes, appeared to have been used within the recommended WHO DDD (Tables 4.17 and 4.18). While some of the less commonly used

agents such as colistin, meropenem, cefepime and ertapenem which were used to treat multidrug resistant *Acinetobacter baumannii*, CREs and *Pseudomonas* were used at high doses and for a longer duration of 10 – 14 days, hence a high average daily DDD/WHO DDD high ratio. However, even though DDD is the most widely used and reliable method of quantifying volume of drug consumption and also recommended by WHO it has its own limitations especially the WHO assigned DDD. The ATC/DDD methodology possesses advantages over other methods of quantifying drug consumption especially in developing countries, but it also requires some minor corrections regarding WHO assigned DDD. However, WHO Collaborating Centre for Drug Statistics Methodology Oslo, which is responsible for assigning ATC codes and DDD to drugs, periodically review DDD of drugs when it receives comments or suggestions for review (WHO, 2016a). For instance it has been documented in the literature that the IV form of amoxicillin/clavulanic acid which is given at 1.2g three times daily has a WHO DDD of 3g, while the oral form which is given at 1g twice daily has a DDD of 1g (WHO, 2016a). This is probably the reason why the average daily DDD/WHO DDD ratio of oral amoxicillin/clavulanic acid appears to be on the high side (Tables 4.17 and 4.18). The WHO DDD for IV amoxicillin/clavulanic acid used to be 1g like the oral form, until 2005 when it was changed to 3g, because of proposals for review (Muller *et al.*, 2006) The average daily dose represents the daily maintenance dose of drug received by a patient, while the average PDD represents the daily amount of a drug that is actually prescribed. The PDD does not reflect actual drug utilisation, because some of the prescribed medications are not always dispensed, and the patient does not always take all the medications that are dispensed (WHO, 2003). This is the reason why PDD was not used to quantify drug consumption in this study.

5.3.2 **Route of administration**

AMS programmes encourage an early switch from IV to oral formulation as soon as the patient can tolerate oral administration especially with agents that have high bioavailability such as fluoroquinolones (Sartelli *et al.*, 2016a). Decreased use of IV antibiotics is associated with reduced LOS (Shrayteh *et al.*, 2014). In this study, most antibiotics were administered intravenously in both stages with a slight reduction during the intervention stage (Tables 4.9 and 4.10). The high use of IV route in this study may be because the study was conducted in a

surgical setting. Patients in some surgical settings, on cancer therapy and those with gastrointestinal conditions especially those that interfere with absorption are associated with increased use of intravenous antibiotics (Shrayteh *et al.*, 2014). The perception that drugs delivered intravenously tend to work faster and effectively compared to those delivered orally, even when a patient can tolerate oral doses could have increased the use of IV antibiotics.

This ignores the cost implications of using administration sets and possibly IV fluids, as well as the risk of developing local and even systemic infections associated with this route. IV routes also require some expertise and extra time to set-up which amounts to an additional cost to both the hospital and patients, especially in the private hospital setting. Researchers in three Lebanese academic hospitals also found a higher use of IV antibiotics, where 79.4% of patients received their antibiotics intravenously, while 20.6% received theirs via oral and IV antibiotics simultaneously (Shrayteh *et al.*, 2014). Other studies have also shown a high use of IV administrations where around 60% to 65% of antibiotics were delivered via this route (Ingram *et al.*, 2012; James and Venu, 2016). The use of oral antibiotics was found to be very low in a Hungarian ICU with about 6.9% and 4.4% in control and post-intervention stages, respectively (Peto *et al.*, 2008). This would be acceptable since most of the cases in ICU were critical and cannot tolerate oral medications.

Table 5.1: AMS studies that showed improvement of antibiotic consumption.

S/N	Study	Setting	AMS Intervention	Outcome
1.	Peto *et al.*, 2008	Surgical ICU of the University of Szeged, Academic Hospital Hungry.	Formulary restriction, Daily bed side consultation 24-hour, Telemedicine consultation.	Reduced antibiotic consumption from 162.9 to 101.3 DDDs/100 patient days.
2a.	Taggart *et al.*, 2015	Trauma/Neurosurgery ICU of an academic hospital in Toronto.	AMS audit and feedback.	Reduction in antibiotic consumption from 1,433 to 1,037 DDDs/1000 patient days.
2b.	Taggart *et al.*, 2015	Surgical/Medical ICU of an academic hospital in Toronto.	AMS audit and feedback.	Increase in antibiotic consumption from 1,705 to 1,936 DDDs/1000 patient days.
3.	Hou *et al.,* 2014	Chinese tertiary hospital ICU.	Formulary restriction, Preauthorisation, Perioperative quinolone restriction.	A 27.44% reduction in an antimicrobial consumption from 197.7 to 143.4 DDDs/100 patient days.
4.	Cisneros *et al.*, 2014	Spanish tertiary hospital ICU.	Local guidelines and educational intervention.	A reduction in antibiotic consumption from 1,150 DDDs/1000 patient days in the 1st quarter of the programme to 852 DDDs/1000 days 4th quarter.

5.3.3 **Duration of therapy**

There was an improvement in DoTh in this study (Tables 4.5 and 4.6). There was a statistically significant reduction (p = 0.01) in the DoTh among patients who had antibiotics for two days and more between the two stages of the study. The average DoTh for patients who received antibiotics for two days and more in the baseline and intervention stages was 4.74 ± 4.58 days and 3.96 ± 2.04

days, respectively, 6.19% of patients had DoTh for >7 days in the baseline stage compared to 2.07% in the intervention stage (Tables 4.5 and 4.6). In this study the duration of antibiotic therapy for *Pseudomonas* and *Acinetobacter* of up to 10 – 14 days is considered appropriate. The reduction in DoTh was expected as during AMS rounds the researcher encouraged source control and early discontinuation of antibiotic treatment. It was also recommended that the consumption of antibiotics should be reduced in patients waiting for surgical operations, especially when there was no clear indication for antibiotic therapy. James and Venu (2016) reported a duration of therapy of up to 15 ± 7.9 days in some surgical cases in a Gastroenterology Unit of an Indian Hospital, this was longer than the DoTh in the General Ward in this current study, which consisted of a large proportion of a gastroenterology cases.

There are controversies about the DoTh in patients with complicated intra-abdominal infections, where the Surgical Infection Society and IDSA recommends 4 to 7 days of therapy, except in cases where there is difficulty in achieving source control (Solomkin *et al.*, 2010). Similarly, the French guidelines propose 5 to 7 days of therapy (Montravers *et al.*, 2015). The World Society of Emergency Surgery has advocated short DoTh in patients with resolved fever and leucocytosis (Sartelli *et al.*, 2013). It has also been a recommendation to decrease the DoTh with antibiotics except in situations that require prolonged treatment, as in cases of immunocompromised individuals or those with ongoing sepsis. If features of sepsis persist after 5 to 7 days of therapy, a septic workup should be considered to determine the focus of infection or antibiotic treatment failure (Sartelli *et al.*, 2016a).

5.3.4 **Appropriateness of antimicrobial prescription**

In this study the appropriateness of antibiotic therapy was determined using Gyssen's algorithm. Gyssen's algorithm assesses appropriateness of antibiotic therapy beyond the use of microbiology results. It considers other parameters such as choice of agent, duration of therapy as well as the cost effectiveness of the therapy i.e. the use of less expensive agents instead of more expensive agents etc. (Figures 4.15 and 4.16). For instance, a culture result may show both a narrow- and broad-spectrum and could be used for target therapy. Cisneros *et al.*, 2014, show that targeted therapy could be inappropriate if

agents are not appropriately selected, or if an agent was not given over an appropriate duration, which is one of the parameters Gyssen's guideline assesses. In the Cisneros' study the percentage inappropriate targeted therapy improves between stages of the study (Cisneros *et al.*, 2014). This shows that the use of Gyssen's algorithm and microbiology results in this study is superior to the use of microbiology result alone, to determine the appropriateness of antibiotic prescription. Overall, there was a statistically significant reduction in the inappropriate antibiotic utilisation in this study from 35% in the baseline stage to 26% during the intervention stage (p = 0.006) using a guideline developed by Gyssens and colleagues (Plenat *et al.,* 1992) (Figures 4.13 and 4.14, Appendix 4). Among the patients who received antibiotics for treatment purposes (empiric/targeted), there was a reduction in inappropriate utilisation during the intervention stages (Figures 4.19 and 4.20). There are limited studies conducted to determine the appropriateness of antibiotic therapy in surgical settings especially in developing countries (Lim *et al.*, 2015). A literature search does not find any AMS intervention study conducted in a surgical setting in South Africa, which was why this study was conducted. However, a personal communication with Prof Mendelson found that there is one currently going on at Groote Schuur Academic Hospital Cape Town (Personal communication). A study conducted in two surgical wards of a Malaysian tertiary hospital, in which appropriateness of antibiotic therapy was determined using a different guideline found that 42.0% of antibiotic used for treatment purposes was inappropriate (Lim *et al.*, 2015). The proportion of inappropriate utilisation for treatment purposes in a Malaysian study was higher than what was found in this study.

A study in five public hospitals in Lesotho, in which appropriateness of antibiotic prescription was assessed also using a different guideline found that 32.2% and 78.4% of the empirically prescribed antibiotics were appropriate among inpatient and outpatient cohort, respectively (Adorka *et al.*, 2014). It has been reported previously that both public and private ICUs across South Africa, had a high percentage of inappropriate usage of antibiotics, where 43.5% and 60.8% of prescriptions were inappropriate in public and private ICUs, respectively (Paruk *et al.*, 2012). This is higher than observed in the current study, possibly due to the study being conducted in the ICU setting where higher antibiotic consumption is likely.

Other studies using the guideline by Gyssens and colleagues (Plenat *et al.,* 1992) also reported higher a percentage of inappropriate prescription, and researchers in an Australian tertiary centre found that 47% of all prescriptions were inappropriate and were mostly due to unjustified prescriptions 35%. Though that was not an intervention study, the percentage of inappropriate prescription was 12% higher than the baseline stage of this study. It further showed that 56% of prescriptions in Vascular, 43% in General and 56% in Gastroenterology/Hepatology units were inappropriate with the underlying reasons being similar to those in this study (Ingram *et al.*, 2012). In a Gastroenterology Unit of an Indian Tertiary Hospital the Gyssen's guideline was implemented and it was reported that 39.9% of all antibiotics were inappropriately used; where the percentage of inappropriate prescriptions was slightly higher 35% than the percentage of inappropriate prescriptions in baseline stage of the current study (James and Venu, 2016). A point prevalence study at a tertiary hospital in Netherlands found that 29.3% of all antibiotic prescriptions usage were inappropriate and mostly was due to unjustified prescriptions (Akhloufi *et al.*, 2015).

A high proportion of inappropriate antibiotic utilisation was seen in patients who received antibiotics for surgical prophylaxis in both stages of the study. Where 64.75% and 61.54% of the prophylaxis were inappropriate in the baseline and intervention stages, respectively, based on wrong choice of agents (Tables 4.27 and 4.28). While 7.34% and 6.59% were inappropriate in the baseline and intervention stages, respectively, based on the duration of more than 24 hours (Section 4.4.4). A high percentage of inappropriate surgical prophylaxis was because of the wrong choice and prolonged duration of prophylaxis where amoxicillin/clavulanic acid was the most frequently used prophylactic agent in both stages. Amoxicillin/clavulanic acid is not recommended for surgical prophylaxis by SAASP and the Standard Treatment Guidelines and Essential Medicines Lists for South Africa, in all the type of procedures conducted in both stages of the study (NDoH 2015; Wasserman *et al.,* 2014). Surgical prophylaxis aims to reduce SSIs which are mostly Gram-positive. The high Gram-negatives prevalence in South Africa is from invasive infections not SSIs. Amoxicillin/clavulanic has an excellent Gram-negative cover which is considered unnecessary for surgical prophylaxis. On the other hand, cefazolin,

aside from its cost-effectiveness, is considered the gold standard surgical prophylactic agent in many surgical prophylactic guidelines, due to its favourable pharmacokinetic profile and the broad cover it has against both Gram-positive and -negative bacteria, except for *Enterococcus* (Bratzler *et al.*, 2013; Kusaba, 2009). The results from this study and many other studies across South Africa have shown that Gram-negative bacteria were the most prevalent pathogens (Brink *et al.*, 2007; Greatorex and Oosthuizen, 2015).

In a Malaysian study 66.3% of prophylaxis were determined to be inappropriate, and 34.5% of inappropriate prophylaxis was due to inappropriate duration and 16.4% was due to wrong choice (Lim *et al.*, 2015). This is similar to the findings of this study (Tables 4.27 and 4.28). Even high inappropriate prophylactic usage was found in other surgical settings, a study in a Jordanian cardiac surgery centre, found that up to 98.3% of surgical prophylaxis was inappropriate based on wrong antibiotic choice, while 58.9% was inappropriate because of duration of more than 48 hours as recommended by the guideline (Al-Momany *et al.*, 2009). A study in a private surgical setting in India found that 32% of surgical prophylaxis was inappropriate because the agents were inappropriately chosen while 37% was inappropriate due to prolonged duration of prophylaxis (Parulekar *et al.*, 2009). China, another BRICS country, adopted an AMS programme in 2012 to encourage appropriate antibiotic utilisation (Xiao and Li, 2013). A study conducted across Chinese provinces showed a reduction in inappropriate surgical prophylaxis (mostly due to incorrect choice of antibiotic) for clean surgeries from 44.38% in 2011 to 33.25% in 2012 (Zhou *et al.*, 2016). Based on the CMAJH drug price list and the South African National Price Catalogue, amoxicillin/clavulanic acid is 2.5 times more expensive than cefazolin where, 1g of cefazolin costs R 8.27 (US$ 0.56) while 1.2g of amoxicillin/clavulanic acid cost R 20.31 (US$ 1.37) (Appendix 5). Two grams of cefazolin is the recommended prophylactic dosage in most of the surgical cases seen in the Vascular and General Wards, so the use of cefazolin apart from being recommended in the guidelines, is also cheaper for the patients and hospital. This intervention brought about little reduction in inappropriate surgical prophylaxis, because the drugs were mostly started in the theatre before they were admitted to the ward where the intervention took place. Prophylactic antibiotics were reviewed during a weekly round where recommendations were

made to change the patient's antibiotic or to stop therapy if the patient has been receiving them for more than 24 hours. In the baseline stage, the main factors associated with inappropriate antibiotic utilisation were the use of less effective agents instead of more effective drugs, unjustified prescriptions, use of more expensive agents and use of more broad-spectrum antibiotics (Figure 4.15). In the intervention stage the use of less effective agents instead of more effective, use of more expensive agents, unjustified prescription and use of more broad agents instead of less broad-spectrum agent were attributed with inappropriate prescriptions (Figure 4.16).

Inappropriate use of antibiotics was high amongst patients who received it for prophylaxis compared to those who received it for treatment purposes, where 64% and 59% of the prophylactic antibiotic usage in baseline and intervention stages was classified as inappropriate (Figures 4.17 and 4.18). For the antibiotics used for treatment (targeted/empiric), 21% and 18% were inappropriate in the baseline and intervention stages, respectively (Figures 4.19 and 4.20). This study concurs with an Australian study where the percentage of inappropriate antibiotic utilisation was high among the patients who had it for prophylaxis 63% compared to those that received it for treatment purposes (empiric and targeted) 52%. The high inappropriate antibiotic usage was largely due to wrong agent choice and unjustified use (Ingram *et al.*, 2012). Researchers at the New York Hospital for Joint Diseases found no difference in likelihood of developing SSIs among patients who had antibiotic prophylaxis for 24 hours and those who had prophylaxis for the entire period they had a surgical drain after spinal procedures (Takemoto *et al.*, 2015). The findings of this New York study showed that prolonging the duration of surgical prophylaxis does not offer additional benefits to the patient and consequently results in the selection of resistant pathogens and additional cost.

5.4 PREDICTORS OF APPROPRIATENESS OF ANTIBIOTIC THERAPY

In this current study, a binary logistic regression model was used to predict the factors associated with the appropriateness of antibiotic prescription. In the crude model increasing age, decreased DoTh, dirty surgical procedures compared to clean-contaminated procedures, use of microscopy/culture, having diagnoses of pancreas, spleen and appendix cases compared to gallbladder,

biliary tract and liver cases and Gram-positive/-negative and fungi were associated with the odds of having an appropriate antibiotic. All these variables except Gram-positive/-negative and fungi were statistically associated with the appropriateness of antibiotic prescription in the crude model (Table 4.29). However, in the adjusted model, it was only age, DoTh, and type of surgery that were statistically associated with predicting appropriateness of prescription. A multivariate logistic regression showed that culture directed therapy was linked with high odds of getting appropriate antimicrobial therapy. While, carbapenems and macrolides usage, antibiotic treatment in patients with creatinine levels of more than 120 µmol/L and the presence of joint/bone disease were statistically associated with an increased odd of receiving inappropriate therapy (Ingram *et al.*, 2012).

It was also determined using logistic regression that previous antimicrobial treatment and age are variables related to inappropriate empiric antimicrobial treatment in patients with a UTI (Velasco *et al.*, 2010). In China, a binary logistic regression was used to predict factors associated with the odds of adhering to the recommendations of the National AMS programmes on surgical prophylaxis in patients with clean operations (Zhou *et al.*, 2016). Geographic region (i.e. province) and hospital bed capacity were significant predictors in both univariate and multivariate models, where hospitals in the western provinces had better outcomes compared to those in the central provinces. On the other hand, hospitals with a bed capacity of less than or equal to 500 had better outcomes compared to those with bed capacity of more than1500 (Zhou *et al.*, 2016).

5.5 PREVALENCE OF PATHOGENS

Laboratory medicine plays a critical role in the success of any AMS programme; it also helps in determining the appropriateness of antibiotic therapy. MCS guides the selection of the right antimicrobial agent, and provides an avenue to either streamline the empiric treatment to a narrow agent if the initial drug was too broad or to escalate to a broad-spectrum if the agent used was too narrow (Sartelli *et al.*, 2016a). Gram-negative bacteria were the most common pathogens in both stages of the study, followed by Gram-positive bacteria. There was a reduction in the culture yield of mixed isolate/normal flora in the Vascular Ward during the intervention stage. This represented a shift from

collecting a superficial specimen to tissue/fluid during the intervention stage. Although this is a more invasive procedural change for the patient, the advantage is that the causative agent is identified and can be more appropriately treated.

In both stages of the study *E. coli*, *P. aeruginosa*, *K. pneumoniae* and *A. baumannii* were the most prevalent pathogens (Tables 4.19 and 4.20) and were mostly cultured from specimens of the General Ward. The prevalence of *P. aeruginosa* and *K. pneumoniae* in the intervention stage increased mostly in the General Ward. It was observed in this study that MSSA was the most frequently cultured bacteria from superficial abscesses, but patients were usually started on empiric amoxicillin/clavulanic acid. *A. baumannii*, *K. pneumoniae*, and *Enterococcus faecium* were the most common resistant pathogens requiring the use of last resort antibiotics such as carbapenems or colistin in both stages of the study (Tables 4.21 and 4.22). Greatorex and Oosthuizen (2015) in Kwazulu-Natal, South Africa, found a high preponderance of Gram-negative bacteria in an ICU where 27% of cultured pathogens were *K. pneumoniae,* 22% *E. coli*, and 17% *Acinetobacter baumannii*. The resistance rate of *K. pneumoniae* to first- and second-line antibiotics was higher - ampicillin 97%, amoxicillin/clavulanic acid 35%, ciprofloxacin 43%, piperacillin/tazobactam 12% but resistance to ertapenem and colistin was 0%. *E. coli* was 79% resistant to ampicillin, 4% to amoxicillin/clavulanic acid and meropenem with 0% resistant rate to piperacillin/tazobactam, ertapenem and colistin (Greatorex and Oosthuizen., 2015). Similarly, Gram-negative bacteria such as *K. pneumoniae*, and *E. coli* were the most frequently isolated bacteria in a study in the South African private health setting. *E. coli* was 84% resistant to ampicillin and 20% to fluoroquinolones, while *K. pneumoniae* showed a regional variation in resistance to ceftriaxone/cefotaxime of 39% to 87% (Brink *et al.*, 2007). A study conducted in a tertiary hospital in southern Netherland involving gastrointestinal surgical cases show a similar prevalence of pathogens with this study, where *E. coli* 25% and *P. aeruginosa* 10% were the most prevalent pathogens (Ramcharan *et al.*, 2014).

A sentinel survey across the United States and Canadian hospitals shows that *S. aureus* and *E. coli* were the most common pathogens causing blood stream infections followed by coagulase-negative *Staphylococci* and *Enterococcus* species (Pfaller *et al.*, 1998). Similarly, *S. aureus* was the most prevalent bacteria causing infections in a Hungarian ICU and most of the cases were MRSA (Peto *et al.*, 2008). In 2005, a surveillance study across hospitals in England also found *S. aureus* as the major cause of SSIs among patients who underwent total hip replacement, in which it was implicated in 50% of the cases, and 59% of these cases were due to MRSA (Ridgeway *et al.*, 2005). Whilst in other countries MRSA is a leading pathogen, its prevalence in this study was low. The results from this study showed an increased request of fluid/tissue and blood culture in the intervention stage (Table 4.26); where the most common specimens requested in the baseline stage were blood, urine followed by fluid/tissue. On the other hand, in the intervention stage, fluid/tissue was the most commonly requested specimen followed by blood and urine. This showed an increase in the request of biological specimens, which contributed towards improvement in appropriateness of antibiotic utilisation in the intervention stage.

Despite high inappropriate antibiotic usage in developing African countries, the prevalence of *C. difficile* infection is low compared to developed countries. The prevalence of *C. difficile* infection in this study was low with 3.13% and 3.85% in the baseline and intervention stages, respectively (Tables 4.19 and 4.20). The findings were similar to results from other studies across Africa - for instance in the Vhembe region of the Limpopo province a prevalence of *C. difficile* of 7.1% was reported (Samie *et al.*, 2008). Similarly, at Bugando and Sekou Toure hospitals in Tanzania the prevalence of *C. difficile* was 6.4% where all patients had a preceding history of antibacterial therapy before the onset of diarrhoea (Seugendo *et al.*, 2015). In neighbouring Zimbabwe, the prevalence of *C. difficile* among the stool samples collected from patients attending hospitals in Harare aged two years and above was 8.6% (Simango and Uladi, 2014). However, a higher prevalence than what was seen in African countries was found in a Peruvian academic hospital, where 35.2% of hospital-acquired diarrhoea in both medical and surgical units was caused by *C. difficile* - this was even higher than what is seen in developed countries (Garcia *et al.*, 2007).

At a geriatric unit of the University of Hamburg academic hospital Germany, 16.4% of asymptomatic patients tested positive for toxigenic *C. difficile* on geneXpert (Nissle *et al.*, 2016). A study in the United Kingdom showed that, reduced consumption of cephalosporins and fluoroquinolones in two hospitals led to a significant reduction in the prevalence of *C. difficile* infection from 280 cases/year in 2007/2008 to 72 cases/year in 2011/2012 (Sarma *et al.*, 2015). Dancer *et al.* (2013) reported a 77% reduction in the prevalence of *C. difficile* infection at a district hospital in Glasgow, over a two-year period after implementation of an antibiotic restriction programme. The programme led to a 95% decrease in the consumption of ceftriaxone from 46.21 to 2.13 DDDs/1000 patient days and 72.5% decrease in ciprofloxacin consumption from 109.80 to 30.21 DDDs/1000 patient days.

These results also showed that the request of culture before commencement of antibiotics was low in both stages of the study. The low requests of culture before the commencement of antibiotics could be explained by the fact that CMJAH receives many patients already on antibiotics from other centres. Often, these patients are apyrexial and are therefore changed empirically without cultures. Usually, cultures are only taken with spiking temperatures. Cultures can and must be taken before antibiotics are commenced in moribund patients.

5.6 COMPLIANCE TO AMS RECOMMENDATIONS

This study showed high compliance to recommendations made during AMS rounds, with 71.18% of recommendations implemented by the surgeons. Though this study has shown a good compliance rate, this was lower when compared to what was seen in other studies. For instance, at the Médecins Sans Frontières medical centre Jordan, there was an increase in compliance to AMS team recommendations from 78% in the first quarter to 97% in the fourth quarter of 2014 (Bhalla *et al.*, 2016). In Spain, compliance had increased from 89% at the inception of the program in 2009 to 93% in 2011. The compliance rate was higher possibly because the intervention was carried out for a longer period than the current study (Del Arco *et al.*, 2015). An AMS programme designed to guide utilisation of antifungal agents at a French academic hospital reported an 88% adherence rate (Mondain *et al.*, 2013). There was no resistance from the surgeons or other professionals in the wards during this

study. However, it was observed that some of the recommendations made at the beginning of the programme such as collection of appropriate samples for culture were not complied with, probably because some doctors were not aware of the programme. This was discussed with the consultants in charge of the units and thereafter compliance rate improved. It is also believed that active participation of senior consultants in AMS rounds, training and practical teaching could have increased the compliance rate. In Cape Town, all efforts of the AMS team to persuade consultants to participate in weekly round failed. Consequently, it was suggested that the residents who participated in rounds are better trained in rational antibiotic usage than their consultants (Boyles *et al.*, 2017). After the implementation of an AMS programmes in China, one of the countries with the highest percent of inappropriate antibiotic utilisation in the world, prescribers in public hospitals faced serious penalties for their failure to adhere to antibiotic prescription guidelines (Bao *et al.*, 2015).

5.7 COST

5.7.1 Cost of antibiotic utilisation

The results showed that the average costs of antibiotics per patient in the Vascular Ward had reduced in the intervention stage from the baseline stage, while in the General Ward it increased in the intervention stage. The cost increment in the General Ward during intervention stage was likely due to costs incurred by the increase in the consumption of more expensive antibiotics such as piperacillin/tazobactam and ertapenem. There was greater detection of resistant organisms in the intervention stage because more cultures were requested hence more targeted therapy (Section 4.3.2).

The total cost of piperacillin/tazobactam and ertapenem increased during the intervention stage compared to the baseline stage in both wards. There was no statistically significant difference in the overall cost of antibiotics between the two stages of this study (p = 0.21). Although ertapenem was not among the five most commonly used agents in the baseline stage, its utilisation increased during the intervention stage for culture directed treatment. A single dose of 4.5 g piperacillin/ tazobactam which is usually given 6 hourly, cost R 53.99 (US$ 3.65) and a dose of ertapenem which is usually given as a daily dose, cost R 368.33 (US$ 24.90), while a dose of amoxicillin/clavulanic acid cost R 20.31

(US$ 1.37) and R 1.81 (US$ 0.12) for IV and oral formulations, respectively (Appendix 5). Based on the latter costing, amoxicillin/clavulanic acid was the most commonly used agent in both stages of the study. In the Cape Town study, there was a 35% reduction in total cost of antibiotics from R 1,068, 328 (US$ 72,233) in the baseline stage to R 373,620 (US$ 25,262) during the intervention stage (Boyles *et al.,* 2013). Recent results of an extension to a 5-year AMS study conducted in Cape Town, showed a substantial reduction in the cost of antibiotics from R 2,191,594 (US$ 148,181) in the pre-implementation stage to R 1,187,942 (US$ 80,321) in the implementation stage, i.e. a R 1,003,652 (US$ 67,860) saving for the hospital and patients (Boyles *et al.*, 2017).

An AMS programme which also looked at costs was introduced at the Médecins Sans Frontières, Medical Centre Amman in Jordan, which receives surgical war victims from Iraq, Syria and Yemen. The programme was driven by a non-specialist medical doctor and a pharmacist with the support of an infectious diseases specialist and involved a weekly antibiotic round. This led to a reduction of antibiotic cost from US$ 252,077 (mean cost US$ 21,006 per month) in the baseline stage to less than US$ 159,948 (mean cost US$ 13,329 per month) in the intervention stage (Bhalla *et al.*, 2016). Implementation of an AMS programme in a hospital in the United States resulted in a substantial reduction in the cost of antibiotic from US$ 4,028,068 in 2010 to US$ 2,135,173 in 2013 (Timbrook *et al.*, 2016). A remarkable reduction in the cost of antibiotics was noted after implementation of an AMS programme in a Saudi Arabian hospital, involving many departments including surgery. A sum of US$ 326,020 was saved monthly because of decreased antibiotic consumption from restricted lists (Alawi and Darwesh, 2016). The two stages of this study were conducted between Febuary and September 2016 at a time when the exchange rate of South African Rand (R) to the United State Dollar was at an average of R 14.79 to US$ 1 (Oanda, 2017). Thus the cost benefit of such a programme has generally been shown to lead to improvements and can assist hospitals with restricted funding to manage more patients with increased efficacy and improved outcomes.

5.7.2 Cost of laboratory investigation

The results showed an increase in the cost of laboratory investigations per patient in the intervention stage. However, this was not due to increase in the cost of the test but rather due to an increase in the request of cultures and biomarkers during AMS rounds (Tables 4.31 and 4.32). Biomarkers such as CRP and PCT were requested during AMS ward rounds especially in cases where surgeons requested superficial cultures which mostly yielded polymicrobial organisms on culture, making it difficult to reach any decision. The increase in the cost of laboratory investigations during the intervention stage concurred with the findings of a previous study. In the Cape Town study, there was an increase in the total cost of laboratory investigations from R 463,580 (US$ 31,344) at the baseline stage to R 608,232 (US$ 41,125) during the implementation stage; which was also due to an increase in the utilisation of biomarkers in the intervention stage (Boyles *et al.,* 2013). The cost of laboratory investigations in the 2017 Cape Town study also increased from R 504,333 (US$ 34,099) in 2011 to R 575,144 (US$ 38,887) in 2015 (Boyles *et al.*, 2017).

5.8 STUDY LIMITATIONS

There were number of limitations to this study which included the following;

5.8.1 Lack of electronic patient records - in this study, data from patient records were manually captured on data collection sheets, transferred to excel spreadsheets, cleaned and analysed. Unlike in the private healthcare sector in South Africa or other countries with established databases where patients' information can be exported directly and transferred to a spreadsheet for analyses - this was a laborious and tedious exercise, which considerably prolonged the duration of data collection. Additionally, the absence of computerised electronic prescription platforms in the study wards made it difficult to monitor recommendations compliance rates. Currently electronic data capturing is being piloted in the public healthcare sector in South Africa as part of a nation-wide roll-out programme from the NDoH which will improve data collection substantially for studies such as this (Personal communication – cluster of Sector Wide Procurement NDoH).

5.8.2 Reproducibility – although the study has led to an improvement in the appropriateness of antibiotic utilisation and a, reduction in the volume of

antibiotic consumption and cost in certain wards, it may be difficult to replicate in many South African public sector hospitals and other hospitals across Africa, outside of the academic setting. This is because of the limited number of infectious diseases physicians in the continent, hence the need to train other professionals. Also, the availability of laboratory and other diagnostic facilities at CMJAH, aided monitoring of biomarkers and drug toxicity levels which led to the success of this study, whereas such facilities are absent in many hospitals across the continent (Boyles *et al.*, 2013).

5.8.3 Generalisability – it is difficult at this point to draw any conclusion based on the findings of this study about antibiotic utilisation in South Africa in general, because the study was conducted in only two wards of a surgery department in a tertiary health centre. Additional studies are required specifically in the surgery setting as well as in other wards and in other hospitals across South Africa.

5.8.4 Even though the study has led to the reduction in antibiotic consumption, which is an important driver that encourages the development of AMR, it is not possible to say this study has led to the reduction of AMR. It was not assessed during the study period which was deemed too short to generate a meaningful conclusion regarding changing resistance patterns. Additionally, in a referral hospital such as the CMJAH which receives patients harbouring multi-drug resistant pathogens from other South African hospitals and across Africa, unless there is proper screening at the point of entry, it is difficult to attribute any reduction in resistance rate to the success of AMS programme (Boyles *et al.*, 2013).

5.8.5 A weekly round is insufficient to adequately monitor antibiotic therapy. Patients who had antibiotics and were discharged after spending a few days in the ward may not have been seen by the AMS team. In addition, patients receiving prophylactic antibiotics mostly received treatment prior to being admitted to the ward, e.g. if patients had a surgical intervention directly from the Emergency Department.

5.8.6 Lack of manpower and poor funding – despite the available data showing the usefulness of AMS programmes in improving patients' clinical outcomes and a

reduction in hospital expenditure, AMS programmes are still challenged with poor funding because of competition with other hospital programmes (Coulter *et al.*, 2015). Hospitals need additional funds to support the personnel who dedicate extra hours to the project (Drew, 2009). Perhaps a further economic evaluation of AMS programmes beyond antibiotic cost savings is required to convince the decision-makers, to support the programme (Dik *et al.*, 2015). A study conducted at a urology unit of a teaching hospital in Holland in which a total of 114 patients receiving antibiotics were reviewed by AMS team on their second day of antibiotic therapy has resulted in a total saving of € 60,306. Whilst the operational cost of implementing the programme including personnel cost was € 17,732 (Dik *et al.*, 2015).

From a survey conducted in France it was determined that the number of professionals required to implement AMS programme was approximately 3.6 infectious diseases specialists' full-time equivalents (FTEs) positions/1000 acute care beds and 2.5 pharmacists FTEs/1000 beds and 0.6 microbiologists FTEs/1000 beds. This totalled 1,960 FTE positions required at the cost of € 200 million per year to implement AMS programmes in French public and private hospitals (Le Coz *et al.*, 2016). In another survey carried out in the United States involving infectious diseases specialists, most of the participants reported that insufficient funding and shortage of personnel were the main challenges affecting successful implementation of AMS (Johannsson *et al.*, 2011). About half of them complained of poor incentives for participating in such programmes (Johannsson *et al.*, 2011). Infectious diseases specialists who often drive AMS programmes were shown to be the least remunerated among 25 major medical professionals in the United States (O'Neill, 2016). An AMS programme implemented at an orthopaedic surgery unit of a German hospital employed the services of an infectious diseases specialist who devoted 10% of his time to the programme at the cost of € 850/ month (Borde *et al.*, 2016).

5.8.7 Inadequate training – high levels of inappropriate antibiotic treatment in surgery are largely due to inadequate training on infectious conditions, and this seems to be true especially of surgeons, probably because rational antimicrobial utilisation in the treatment of surgical infections is not efficiently taught in their training (Çakmakçi, 2015). So, their active participation in AMS projects may

increase the success rate of such programmes (Çakmakçi, 2015). Depriving surgeons of their right to prescribe restricted antibiotics affects their working relationship with the AMS team, hence the need to involve them especially those with a good understanding of surgical infections to audit prescriptions and give feedback to their colleagues (Sartelli *et al.*, 2016b).

5.8.8 Increase of laboratory cost – following the introduction of an AMS programme in Cape Town, an increase in laboratory costs was seen, this was attributed to increased utilisation of biomarkers such as CRP and PCT (Boyles *et al.,* 2013; Boyles *et al.*, 2017). The routine use of CRP and PCT as a way of distinguishing bacterial from acute viral respiratory tract infections in a resource challenged country like South Africa with a high prevalence of tuberculosis is of less benefit as both markers are increased in tuberculosis (Mendelson, 2015a).

5.9 RECOMMENDATIONS

5.9.1 Training – due to a high proportion of inappropriate surgical prophylaxis and high use of IV antibiotics in this study, training such as short courses on surgical prophylaxis and rational antibiotic usage for surgeons and theatre staff is recommended. Additionally, incorporation of AMS courses in the curricula of South African medical, veterinary and other health science students, as some South African schools of pharmacy have started, will prepare the next generation of health professionals to embrace the culture of rational antibiotic prescribing early in their professional career. It is also recommended to include AMS training into curricula of surgery residency programmes as this may increase registrar's understanding of surgical infections.

5.9.2 Multidisciplinary team – it is recommended to form a multidisciplinary team in the hospital comprising of infectious diseases specialists, clinical microbiologists, pharmacists, infection control nurses, and hospital administrative staff. Increased frequency of ward rounds to about 2 to 3 times a week will provide an opportunity to more closely monitor patients on antibiotic therapy. Regional hospitals are also encouraged to implement AMS programmes and liaise with the infectious diseases physicians in academic hospitals to give expert and technical advice.

5.9.3 The hospital is encouraged to continue with the weekly antibiotic round to maintain the successes achieved during the study. Now that the programme is completed, the absence of ongoing AMS ward rounds could allow the process to reverse to where it started. They are also encouraged to develop a computerised decision support system which provides physicians with appropriate treatment options and guides when prescribing drugs which, will improve rational antimicrobial utilisation.

5.10 CONCLUSION

Even though antibiotic resistance is a natural phenomenon and an inevitable event, rational antibiotic prescribing, AMS programmes, infection and prevention control measures will go a long way in slowing or even reversing the fast approaching post-antibiotic era. This study has attempted to provide the clinicians with an overview of antibiotic utilisation and an AMS intervention in a surgical setting of a public South African tertiary health institution. The findings show an improvement in an appropriateness of antibiotic utilisation, reduction in antibiotic consumption and DoTh. In addition, there was reduction in cost of antibiotics in one of the study wards, after implementation of the AMS programme. Also, there was an improvement in culture directed treatment, requests for biological specimens for culture, with a consequent increase in the cost of laboratory investigations per patient due to increased culture requests during the intervention stage. The high rate of AMR especially in developing countries necessitates proactive measures to address the problem; as such a multidisciplinary approach through AMS is an option to address inappropriate antimicrobial use with cost savings in hospitals.

5.11 FUTURE RESEARCH

Further research is required to understand why clinicians and surgeons are not adhering to the local surgical prophylaxis guidelines. Further research is also required to evaluate the importance of AMS interventions in clinical outcomes and long term changes in pattern of resistance. There is a need to conduct studies on SSIs in other clinical setting such as cardiothoracic surgery and orthopaedics. Also, there is a need to conduct a study to assess the impact of increasing frequency of AMS ward round on clinical outcomes. There is also need to repeat this study in the same wards in years' time to see if the successes

recorded now are maintained. Qualitative research would also add value in better understanding what behavioural factors and challenges would need to be addressed to further improve adherence to AMS programmes.

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APPENDIX 1

- **ANTIBIOTICS ATC CODES**
- **Table A.1: Antibiotics ATC codes**

Name of Antibiotics	ATC Code
Amoxicillin/Clavulanic acid	J01CR02
Piperacillin/tazobactam	J01CR05
Cefazolin	J01DB04
Metronidazole	J01XD01
Fluconazole	J02AC01
Vancomycin	J01XA01
Cloxacillin	J01CF02
Imipenem	J01DH51
Ciprofloxacin	J01MA02
Sulfamethoxazole/Trimethoprim	J01EE01
Clarithromycin	J01FA09
Cefepime	J01DE01
Cefotaxime	J01DD02
Linezolid	J01XX08
Amoxicillin	J01CA04
Azithromycin	J01FA10
Clindamycin	J01FF01
Colistin	J01XB01
Amikacin	J01GB06
Ertapenem	J01DH03
Erythromycin	J01FA01
Gentamycin	J01GB03
Amphotericin B	J02AA01
Ceftazidime	J01DD02
Ceftriaxone	J01DD04

APPENDIX 2

- **DATA COLLECTION TABLE ON DEMOGRAPHIC CHARACTERISTICS AND NATURE OF SURGERY**
- **Table A.2: Collection sheet to collate demographic characteristics and nature of surgery of patients.**

Study number	Age	Sex	Ward	DOA	DOD	LOS	Diagnoses	Type of surgery	Number of procedures

APPENDIX 3

- **DATA COLLECTION TABLE ON DRUG UTILISATION**
- **Table A.3: Collection sheet to collate drug utilisation**

Study number	Name of antibiotics	Date 1	Date 2	Duration of therapy (days)	Frequency	Route	Dose	Allergy/ADR	Clinical Indication	Net quantity	Formulation	Strength	WHO DDD	DDDS	DDD/1000 patient day	Cost (ZAR)	Appropriateness	Number of antibiotics per patient

DDD: Defined Daily Doses

Date 1: the day antibiotic started.

Date 2: the day antibiotic stopped

APPENDIX 4

- **GYSSEN'S CRITERIA FOR ASSESSING APPROPRIATENESS OF ANTIMICROBIAL DRUG THERAPY (ADT)**

i. Appropriate ADT.

ii. Inappropriate ADT, due to:
   a. Improper dosage
   b. Improper dosage interval
   d. Improper route

iii. Inappropriate ADT prescription due
   a. Excessive length
   b. Duration of therapy too short

iv. Inappropriate ADT, due to incorrect choice:
   a. More effective agent is available
   b. Less toxic alternative agent is available
   c. Less expensive alternative agent is available
   d. Less broad-spectrum alternative agent is available

v. Inappropriate ADT, due to unjustified prescription (use of any antimicrobial is not indicated).

vi. Insufficient information.

ADT = Antimicrobial Drug Therapy
(Plenat *et al.,* 1992).

APPENDIX 5

- **ANTIBIOTIC PRICE LIST**
- **Table A.4: Table for antibiotic price list**

Name of antibiotics	Price/Package (R)	Price/Dose (R)
Amikacin 500mg	-	4.24
Amoxicillin	-	0.46
IV Amoxicillin-clavulanic acid 1.2g	-	20.31
Oral Amoxicillin-clavulanic acid 500mg	18.1	1.81
Amphotericin B 50mg	-	43.50
IV Azithromycin 500mg	-	46.55
Oral Azithromycin 500mg	14.64	4.88
Cefazolin 1g	-	8.27
Cefepime 1g	-	34.43
Ceftazidime 1g	-	65.89
Ceftriaxone 1g	-	5.84
Cefotaxime 1g	-	32.95
IV Ciprofloxacin 500mg	-	40.52
Oral Ciprofloxacin 400mg	7.25	0.75
Clarithromycin 500mg	69.33	4.95
IV Clindamycin 600mg	-	9.12
Oral Clindamycin 600mg	65.19	3.26
Cloxacillin 500mg	-	13.66
Colistin 2mu	-	41.04
Ertapenem 1g	-	368.33
IV Erythromycin 1000mg	-	200.00
Fluconazole 400mg	-	16.63
Gentamycin 240	-	6.59
Imipenem 1g	-	47.88
Meropenem 1g	-	62.70
IV Metronidazole 500mg	-	5.61
Oral Metronidazole 400mg	12.13	0.43
Piperacillin/tazobactam 4.5g	-	53.99
Sulfamethoxazole/trimethoprim 950mg	15.19	0.15
Vancomycin 1g	-	40.04
Linezolid 600mg	-`	292.03
Nystatin drop	15.16	-

APPENDIX 6

- **DATA COLLECTION TABLE ON MICROSCOPY CULTURE AND SENSITIVITY AND BIOMARKERS**
- **Table A.5: Collection sheet to collate results of microscopy culture and sensitivity and biomarkers**

Study Number	Date 1	Date 2	TSL	Time from sample collection to result to release	Specimen type	Culture Submitted before or after Antibiotic	Microscopy	Pathogens	Susceptible antibiotics	Resistant antibiotics	Recommended Antibiotics	Empiric /prophylactic /directed	FBC	CRP	Procalcitonin	Cost (R)

TSL: Time from Specimen Collection to Result Release

Date 1: the day specimen collected

Date 2: the day result was released by the laboratory

APPENDIX 7

- **LABORATORY INVESTIGATIONS PRICE LIST**
- **Table A.6: Laboratory investigation price list**

S/NO	TYPE OF INVESTIGATION	PRICE(R)
1.	Blood culture	44.02
2.	CSF culture no growth	47.38
3.	CSF culture growth	47.38
4.	Culture anaerobic	33.97
5.	Urine culture	47.38
6.	Lowenstein-Jensen culture	14.33
7.	ZN Mycobacterium isolate on culture	23.11
8.	Fungal blood culture	44.02
9.	Fungal cultures	33.97
10.	Fungal identification	94.07
11.	Culture anaerobic	33.97
12.	Culture aerobic	47.38
13.	Culture for *S. aureus*	17.00
14.	Culture for *Streptococcus pyogenes*	47.38
15.	Faeces/urine culture *S. typhi*	47.38
16.	MIC	91.64
17.	Assay antifungal	106.65
18.	Candida serology	41.37
19.	Microscopy	36.89
20.	*Clostridium difficile* toxin	225.26
21.	PCR for *M. tuberculosis*	530.96
22.	GeneXpert PCR tuberculosis	165.99
23.	FBC	50.16
24.	WBC only	15.60
25.	C-reactive protein	84.71
26.	Procalcitonin	335.98

Source: NHLS State Price List 2015

APPENDIX 8

- **ETHICAL CLEARANCE CERTIFICATE TO CONDUCT A PROSPECTIVE STUDY**

R14/49 Dr Bashar Muhammad Augie

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M151142

NAME: (Principal Investigator)	Dr Bashar Muhammad Augie
DEPARTMENT:	Pharmacy and Pharmacology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Effects of Antimicrobal Stewardship Policy in Improving Antibiotic Utilization and Reducing Drug Costs in a Public Hospital Gauteng Province, South Africa
DATE CONSIDERED:	27/11/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Jaqui Miot, Prof Robyn Van Zyl and Dr Evan Shoul
APPROVED BY:	Professor P. Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	22/04/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

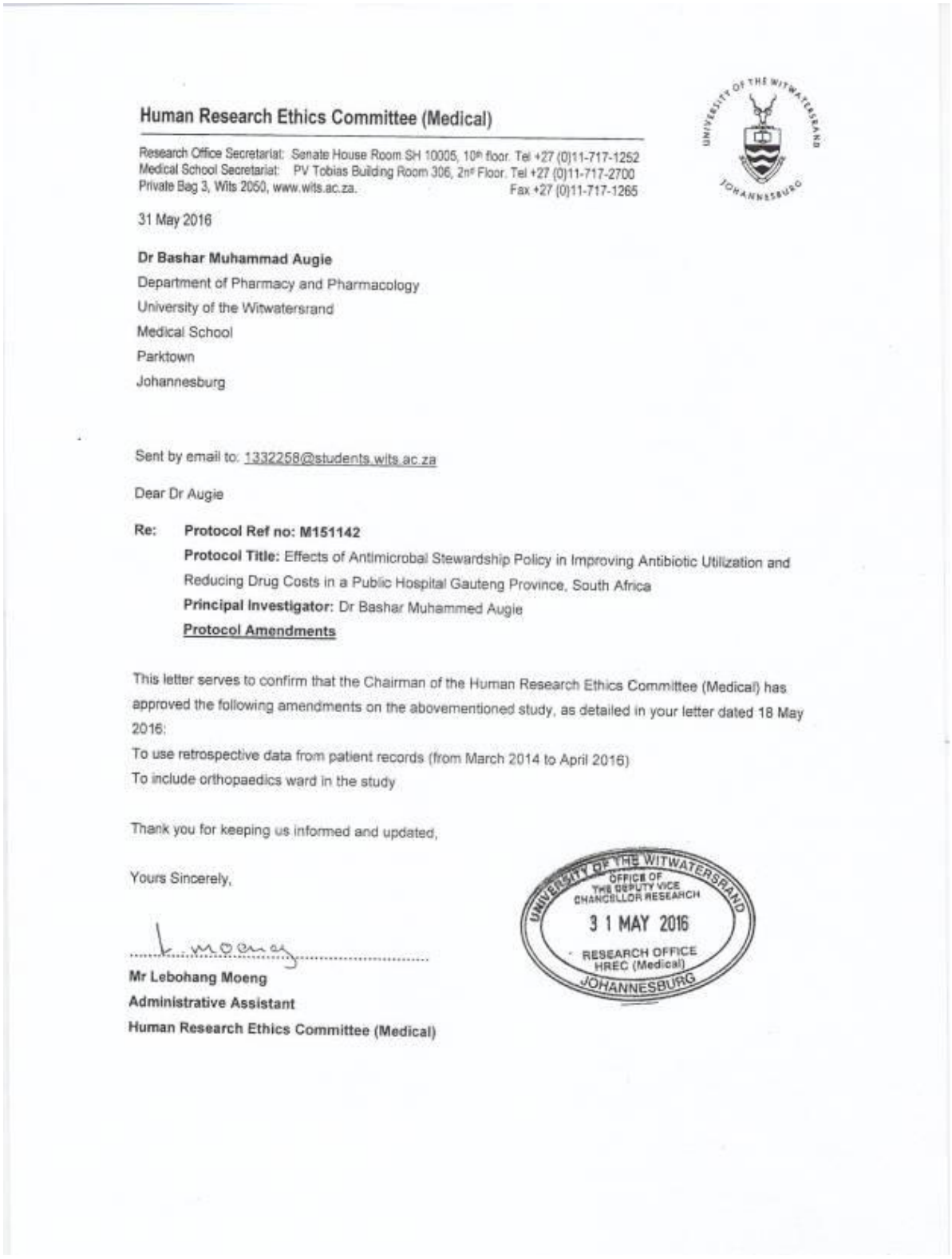
To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004,10th floor, Senate House/2nd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated,from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially review in November and will therefore be due in the month of November each year.

Principal Investigator Signature Date 22/04/2016

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX 9

- **ETHICAL CLEARANCE CERTIFICATE TO CONDUCT A RETROSPECTIVE STUDY**



Human Research Ethics Committee (Medical)

Research Office Secretariat: Senate House Room SH 10005, 10th floor. Tel +27 (0)11-717-1252
Medical School Secretariat: PV Tobias Building Room 306, 2nd Floor. Tel +27 (0)11-717-2700
Private Bag 3, Wits 2050, www.wits.ac.za. Fax +27 (0)11-717-1265

31 May 2016

Dr Bashar Muhammad Augie
Department of Pharmacy and Pharmacology
University of the Witwatersrand
Medical School
Parktown
Johannesburg

Sent by email to: 1332258@students.wits.ac.za

Dear Dr Augie

Re: **Protocol Ref no: M151142**
Protocol Title: Effects of Antimicrobal Stewardship Policy in Improving Antibiotic Utilization and Reducing Drug Costs in a Public Hospital Gauteng Province, South Africa
Principal Investigator: Dr Bashar Muhammed Augie
Protocol Amendments

This letter serves to confirm that the Chairman of the Human Research Ethics Committee (Medical) has approved the following amendments on the abovementioned study, as detailed in your letter dated 18 May 2016:
To use retrospective data from patient records (from March 2014 to April 2016)
To include orthopaedics ward in the study

Thank you for keeping us informed and updated,

Yours Sincerely,

UNIVERSITY OF THE WITWATERSRAND OFFICE OF THE DEPUTY VICE CHANCELLOR RESEARCH 31 MAY 2016 RESEARCH OFFICE HREC (Medical) JOHANNESBURG

Mr Lebohang Moeng
Administrative Assistant
Human Research Ethics Committee (Medical)

APPENDIX 10

- **LETTER OF HOSPITAL PERMISSION TO CONDUCT STUDY**

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Mr. J. Maepa
Office of the Clinical Director
Tell: (011): 488-3365
Email:Johannes.maepa@gauteng.gov.za
13 January 2015

Dear Dr. Bushar Muhammad Augie

STUDY TITLE: Effects of Antimicrobial Stewardship policy in improving antibiotic utilization and reducing drug costs in a public Hospital in Gauteng Province, South Africa.

Permission is granted for you to conduct the above recruitment activities as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic Hospital will not anyway incur or inherit costs as result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall be observed at all times.
4. Informed consent shall be solicited from patients participating in your study.

Please liaise with the HOD and Unit Manager or sister in charge to agree on the dates and time that would suit all parties.

Kindly forward this office with the results of your study on completion of the research.

Supported/~~not supported~~

Dr. M.K Mofokeng
Clinical Director
DATE: 14/01/2016

Approved/not approved

Ms. G. Bogoshi
Chief Executive Officer
DATE: 19-01-2016

APPENDIX 11

- **LETTER OF PERMISSION TO CONDUCT STUDY IN SURGERY DEPARTMENT**

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

University
of the Witwatersrand
Johannesburg

Department of Surgery:

Charlotte Maxeke Johannesburg Academic Hospital

Post net Suite #235, Private Bag x2600, Houghton 2041 • Telephone +27 (0)11 488-3373 • Fax +27 (0)11 488-4322 • Email: Thembekile.mthembu@wits.ac.za

08th December 2015

Ms. G Bogoshi
Office of the CEO
Charlotte Maxeke Johannesburg Academic Hospital

Dear CEO

Re: Research Project:

Good day. This is to inform you that Dr Bashar Muhammad Augie is planning to conduct a study titled:

- Effects of Antimicrobial Stewardship policy in improving antibiotic utilization and reducing drug costs in a public Hospital in Gauteng Province, South Africa.

We are aware of the study and fully support it. There will be no cost implication to the Hospital. Dr Augie has already applied for ethical approval from the Human Ethics Committee of University of the Witwatersrand.

Yours sincerely

Dr T E Luvhengo
Clinical Head of Surgery Department
Charlotte Maxeke Johannesburg Academic Hospital

APPENDIX 12

- **LETTER OF PROTOCOL TITLE APPROVAL**

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

13 April 2016
Person No: 1332258
PAG

Mr MA Bashar
Federal University Bir
Nin Kebbi
PMB 1157
0000
Nigeria

Dear Mr Bashar

Master of Science in Medicine: Approval of Title

We have pleasure in advising that your proposal entitled *Effects of antimicrobial stewardship policy in improving antibiotic utilization and reducing drug costs in a public hospital in Gauteng Province, South Africa* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

APPENDIX 13

- **LETTER OF CONSENT**

Letter of consent seeking patient's permission to review their records.

Effects of Antimicrobial Stewardship policy in improving antibiotic utilisation and reducing drug costs in a public hospital in Gauteng province, South Africa

Good day, Sir/Madam.

My name is Dr. Bashar Muhammad Augie, and I am registered for a Pharmacology Masters (MSc Med) by dissertation at the Faculty of Health Sciences, University of the Witwatersrand. I am conducting this project as part of my master's dissertation and it involves assessing the effect of Antimicrobial Stewardship (AMS) policy in improving antibiotic utilisation and reducing drug costs in a public hospital in Gauteng Province, South Africa, under the supervision of Dr. Jacqui Miot, Prof Robyn van Zyl and Dr. Evan Shoul. I am seeking your permission to review your patient records; this will enable me to determine the impact of an AMS policy in improving antibiotic utilisation and reduction in drug costs. This is a combined prevalence cross-sectional analysis with a prospective observational study.

Your anonymity will be ensured, any information that may reveal your identity such as name and address will not be recorded. A unique study number will be assigned to your records, the list of study numbers and patients record numbers will be kept in a password protected data file and only accessible to me and my supervisors. No patient file will be taken away from the facility nor will any copies of files or patient information be made, so your identity will not be revealed when the study is reported or published.

If you have any questions about the study or participating in the study please feel free to ask me (Bashar Muhammad Augie), you can call me at 060 380 7904 or email me on 1332258@students.wits.ac.za.

Your participation in this study is totally voluntary, you are under no obligation to participate, and you have the right to withdraw at any time if you care to without repercussion or penalty.

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The ethics for the study has been approved by the University of the Witwatersrand Human Research Ethics Committee.

I have discussed the above points with participants; it is my opinion that the participant understands the risks, benefit and obligations involved in participating in this project.

_____ _____

Researcher’s signature Date

I understand that my participation is voluntary and that I may refuse to give permission or can withdraw my consent and stop taking part at any time without penalty.

I hereby freely agree to a review of my patient records.

_____ _____ _____

Signature of participant Signature of witness Date

APPENDIX 14

- **INFORMATION SHEET**

Effects of Antimicrobial Stewardship policy in improving antibiotic utilisation and reducing drug costs in a public hospital in Gauteng province, South Africa

Dear potential participant,

I am Dr. Bashar Muhammad Augie, and I am a master's student in the division of Pharmacology, Department of Pharmacy and Pharmacology, University of the Witwatersrand Johannesburg. I am doing research on the impact of an antimicrobial stewardship policy in improving antibiotic use and reducing drug costs in a public hospital in Gauteng Province, South Africa. This study will take place in the Department of Pharmacy and Pharmacology and the Surgery Department of Charlotte Maxeke Johannesburg Academic Hospital. Antimicrobial stewardship programmes (AMS), have been shown to improve appropriate use of antibiotics in some places with an overall reduction in drug cost and duration of hospital stay. AMS also reduces toxicity from drugs by selecting the most appropriate drug at its correct dosage and route of delivery.

The aim of this study is to describe how antibiotics are currently prescribed and to measure the impact of introducing an antimicrobial stewardship intervention on cost and utilisation in your surgical ward of the Charlotte Maxeke Johannesburg Academic Hospital. I am seeking your permission to review your hospital records where I will capture information on your clinical condition, type of surgery, related blood tests and which antibiotics have been prescribed for you.

Patient records for this study will be selected using a convenience sampling and inclusion criteria will be; patients who give consent for their records to be reviewed, any patient 18 years or older, currently taking an antibiotic for infection or having taken an antibiotic prescribed within the previous 48 hours of the time of capturing information. The exclusion criteria will include pregnant women and patients who have not taken an antibiotic within the previous 48 hours, before capturing of data. Patients are required to give consent before their records will be reviewed. There is no potential risk in participating in this study and potential benefits include an improvement in antibiotic utilisation in the Surgery Department.

Your participation in this study is totally voluntary, you are under no obligation to participate, and you have the right to withdraw your consent at any time if you care to without repercussion or penalty. Your anonymity will be ensured, any information that will reveal your identity such as name and address will not be recorded. A unique study number will be assigned to your records, the list of study numbers and patients record numbers will be kept in a password protected data file and only accessible to the me

and my supervisors. No patient file will be taken away from the facility nor will any copies of files or patient information be made, so your identity will not be revealed when the study is reported or published.

If you have any questions about the study please feel free to ask me (Bashar Muhammad Augie), you can also call me at 060 380 7904 or email me on 1332258@students.wits.ac.za.

For any complaints or problem feel free to contact Administrative Officer: Human Research Ethics Committee (Medical), Ms Zanele Ndolovu on email zanele.ndlovu@wits.ac.za or call on 011 717-1234.

APPENDIX 15

- **SPECIMENS WHICH GREW MULTIDRUG RESISTANT BACTERIA IN THE BASELINE STAGE**
- **Table A.7: Specimens which grew multidrug resistant bacteria in the baseline stage**

Specimens that Yielded Resistant Pathogens	Type of Ward		Total of both Wards n (%)
	Vascular Ward n (%)	General surgical Ward n (%)	
Urine	1(12.5)	9(28.1)	10(25.0)
Blood	2(25.0)	6(18.8)	8(20.0)
Superficial swab	4(50.0)	3(9.4)	7(17.5)
Fluid/tissue	1(2.5)	5(15.6)	6(15.0)
Drain fluid	-	4(12.5)	4(10.0)
Drain fluid (sterile cavity)	-	2(6.3)	2(5.0)
Abscess	-	2(6.3)	2(5.0)
Tissue	-	1(3.1)	1(2.5)
Total	8(100.0)	32(100.0)	40(100.0)

APPENDIX 16

- **SPECIMENS WHICH GREW MULTIDRUG RESISTANT BACTERIA IN THE INTERVENTION STAGE**
- **Table A.8: Specimens which grew multidrug resistant bacteria in the intervention stage.**

Specimens that Yielded Resistant Pathogens	Type of Ward		Total of both Wards n (%)
	Vascular Ward n (%)	General Surgical Ward n (%)	
Urine	2 (16.67)	1 (2.00)	3(4.84)
Blood	1 (8.33)	2 (4.00)	3(4.84)
Superficial swab	3 (25.00)	10 (20.00)	13 (20.97)
Fluid/tissue	3 (25.00)	28 (56.00)	31 (50.00)
Drain fluid (sterile cavity)	-	5(10.00)	5 (8.06)
Sputum	-	1 (2.00)	1 (1.61)
Tissue	3 (25.00)	3 (6.00)	6(9.68)
Total	12 (100.00)	50 (100.00)	62 (100.00)