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LIST OF ABBREVIATIONS

ASP	Antimicrobial stewardship program
AMS	Antimicrobial stewardship
AMR	Antimicrobial resistance
ASPAQ	Antimicrobial stewardship program assessment questionnaire
CDC	Centre for Disease Control and Prevention
ICU	Intensive care unit
IDSA	Infectious Diseases Society of America
HAI	Hospital acquired infection
MRSA	Methicillin-resistant staphylococcus aureus
NDOH	National department of health
WHO	World health organization
MDR	Multidrug resistance
SAASP	South African antimicrobial stewardship program
SHEA	Society of Healthcare Epidemiology of America

CHAPTER 1

ORIENTATION TO THE RESEARCH STUDY

1.1 Introduction

Healthcare-associated infections (HAIs) are a cause of significant morbidity and mortality in patients receiving health care (Brink, Feldman, Duse, Gopalan, Grolman, Mer, Naiker, Paget, Perovik & Richards 2006: 153). Majority of these infections are caused by antibiotic-resistant bacteria which can easily spread (Gould 2011:16). Furthermore, they are difficult to treat and do not respond to standard treatment, leading to prolonged illness, high treatment costs, extended hospitalisation and adverse complications (Cosgrove & Carmeli 2003:1435; Singh, Arora, Thangaraju, Singh & Natt 2013: 95). The increasing challenges to the emergence and spread of resistant bacteria are a global concern and affects both clinical and financial therapeutic outcomes (Essack 2006: 51).

Although the evidence is not of high quality, it has been established that antibiotics are key contributors to the development and spread of antimicrobial resistance (AMR) (Tacconelli 2009: 355: 357). In addition, the driving force of this threat were identified as 1) The misuse of antibiotics by both patients healthcare providers (Tacconelli 2009: 356), (2) a lack of compliance with appropriate antibiotic therapy by patients, such as missing doses or ceasing a course of antibiotics before cure, self-medicating (Pinder, Sallis, Berry & Chadborn 2015:17), (3) Host-susceptibility, which is demonstrated in the very old, the very young, those undergoing invasive procedures, severely ill, immune-compromised patient and those patients staying longer in hospitals (Weinstein 1998:417).

Healthcare settings are associated with the highest emergence and spread of antimicrobial resistance (Pinder et al, 2015: 9). The highest rates are observed in intensive care units (ICU); adult and paediatric ICUs (Weinstein 1998: 147). In South African ICUs, antibiotic prescription habits are far from acceptable and are associated with poor fiscal outcomes, increased mortality and limitations of therapeutic options (Paruk, Richards, Scribante, Bhagwanjee, Mer & Perrie 2012:

615). Therefore, an urgent intervention to curb the emergence and spread of antimicrobial resistant pathogens is imperative in this country.

To counter the emergence and spread of multi-drug resistant pathogens, Duse (2005: 37) recommended the implementation of an effective and integrated programme that involves antimicrobial surveillance, a rational antimicrobial use programme, and infection control. This was corroborated by Bamford, Bonorchis, Ryan, Simpson, Elliott, Hoffmann, Naicker, Ismail, Mbelle, Nchabeleng, Nana, Sriruttan, Seetharam & Wadula (2011: 243) advocating regular surveillance of local antimicrobial susceptibility patterns to provide information on new, or changing, patterns of resistance, and informing clinician on prescribing and selection of empiric therapy.

Despite the recommendations and guidelines from governmental and professional groups, South African infection control programmes are generally poor, ranging from non-existent to excellent (Duse 2005: 39). Good and standardised surveillance systems for HAIs are currently not in place in most healthcare institutions (Brink, et al. 2006:153). Additionally, the monitoring of antimicrobial resistance has been largely neglected (Duse 2005:39).

According to Antimicrobial Resistance Background report, all public hospitals in South Africa have implemented an antimicrobial stewardship programme involving a restricted formulary approach and perform a pharmacy-led ward rounds (NDoH 2015: 11). However, constant impact evaluation of the programme is important to assist in making decision to scaling-up. Although, numerous studies have evaluated the impact of ASPs in health care institutions and provided evidence on the effectiveness of ASPs, there is no evidence of any comprehensive impact assessment on the ASPs implemented in South African hospitals.

This study was therefore aimed at assessing the sustainable effectiveness of the implemented antimicrobial stewardship programme, to identify constraints in its performance to optimise the quality of antimicrobial prescribing and improve patients' outcome.

1.2 BACKGROUND TO THE RESEARCH PROBLEM

South African hospitals are battling with the growing emergence of key antimicrobial resistant pathogens particularly regarding carbapenems (Bamford, Brink, Govender, Lewis, Perovic, Botha, Harris, Keddy, Gelband, & Duse 2011: 250).

In 2001, Global Antibiotic Resistant Partnership published a situational analysis of antibiotic use and resistance in South Africa, suggesting that antibiotic resistance is driven by many factors, many of which are associated with inappropriate antibiotic management and consumption (Gelband & Duse 2001: 552). Further, the authors identified the poor living conditions, shortages of antibiotics to the public sector, the use of previously prescribed antibiotics, and self-diagnosing and over the counter access to antibiotics, as well as clinicians as contributing factors (Gelband & Duse 2011: 552).

Another author pointed out that the poverty-driven practices of medication sharing and self-treatment, resulting in inappropriate choice of medication for the specific organism, and the inappropriate dose or duration of therapy, involving the use of poor-quality and foreign-made drugs, may exacerbate the emergence and spread of multidrug-resistant organisms (Planta 2007: 534- 535). Omulo, Thumbi, Njenga and Call (2015: 1) states that the increased demand for antimicrobial therapies in south Africa, is exacerbated by the occurrence and increase of conditions such as acute respiratory infections, diarrheal diseases, HIV/AIDs, tuberculosis, malaria and helminthic infections .

Resistance to antimicrobial drugs is escalating worldwide including South Africa (Truter 2015: 52). A 2015 study analyzing prevalence of infection and patterns of resistance in critically injured polytrauma patients admitted to a level1 trauma ICU, at a Charlotte Maxeke Johannesburg Academic hospital, indicated Gram-negative organisms as predominant, along with the most common organism as *Pseudomonas* (30.1%), followed by *Klebsiella* (25.7%), *Acinetobacter* (16.4%) as well as *Staphylococcus aureus* infection (5.8%) (Pillai, Yazicioglu, Moeng, Rangaka, Monareng, Jayakrishnan, Veller & Pinkus 2015: 740)

In a review conducted to gather scientific evidence of the extent and patterns of antimicrobial resistance in selected hospital-acquired pathogens, eight manuscripts published between 2000 and 2011 were reviewed and included susceptibility data from four of the nine provinces of South Africa. An overall occurrence of resistance to antimicrobials used was observed and escalating rates of antimicrobial resistance to several conventional antimicrobials, such as the high rates of ESBL and MRSA was detected in these urban academic centres and private institutions (Nyasulu, Murray, Perovic & Koornhof 2012: 9-12)

A study undertaken in a large tertiary hospital in Durban, KwaZulu Natal demonstrated a high overall prevalence of antimicrobial resistant bacteria isolated in adult medical and surgical ICUs, medical and surgical neurosurgery ICU, trauma ICU (TICU), Cardiothoracic ICU (CTC ICU) and the burns unit, indicating MRSA with an average of 64.2%, and ESBL + *K pneumoniae* (63%), MDR Acinebacter species (62.6%) and MDR *Pseudomonas auruginosa* (10.4%) (Swe Swe-Han & Coovadia 2010: 2).

The increasing rate of antimicrobial resistant pathogens is critically compromising the management of common and lethal bacterial infections (GARP-India working group 2011: 282). Consequently, the Infectious Diseases Society of America in 2007 published guidelines promoting the development of an institutional programme in all hospitals to enhance antimicrobial stewardship (Dellit, Owens, McGowan, Jr., Gerding, Weinstein, Burke, Huskins, Paterson, Fishman, Carpenter, Brennan, Billeter & Hooton 2007:159).

In response to the current status of AMR a number of initiatives including Global Antibiotic Resistance Partnership (GARP) in South Africa (Duse 2011: 551), South African Antibiotic Stewardship Programme (SAASP) (Mendelson, Whitelaw, Nicol & Brink 2012: 307), were introduced to address the scourge of AMR. Although, laboratory-based antimicrobial resistance surveillance has been implemented for many years by South African Society for Clinical Microbiology (SASCM) formerly known as National Antibiotic Surveillance Forum (NASF) (Bamford et al. 2011: 243), and Group for Enteric, Respiratory and Meningeal Surveillance (GERMS)-SA

(GERMS-SA 2007: 4), there are still gaps in knowledge about the extent of AMR in South Africa.

Nevertheless, such efforts are flooded with a multitude of limitations which may impede the AMS activities in healthcare facilities. According to the Antimicrobial Resistance Background Report some of the deficiencies include the prescribers' inability to send appropriate clinical samples for culture and sensitivity testing prior to prescribing antimicrobials, a lack of linkage of pharmacy, clinical and laboratory data systems in institutions resulting in poor and incomplete reporting of antimicrobial use as well as a shortage in trained personnel such as microbiologists, AMS practitioners and infectious diseases specialist (NDoH 2015: 15).

Thus, despite the advocacy and initiatives embarked on, South Africa is at the forefront in the prevalence of gram-negative microorganisms that are resistant to beta-lactam antibiotics (extended-spectrum beta lactamases) (Van den Bergh 2009:1). Without a further assessment of the on-going support and relevance of the activities of the ASP, the programme's aim of improving the quality of healthcare and patients care will not be achieved. Even so, there is a scarcity of evidence of the impact of ASP in South Africa, therefore, this situation must be corrected to elucidate and improve on the limitation of the ASP implemented in South African hospitals.

1.3 RESEARCH PROBLEM

Based on the growing evidence of the increasing rate of antimicrobial resistant pathogens in South Africa, the effectiveness of the ASPs implemented in healthcare institutions to promote appropriate antimicrobial use should be evaluated and optimised. Any unattended deficient in the performance of the ASP will render the efforts inadequate to limit the scourge of antimicrobial resistant and improve patients' health.

A comprehensive evaluation of the impact of ASP implemented in hospitals in South Africa is imperative to elucidate any shortfall on its performance. Such evaluation will help in optimising ASP and improving on the quality of the antimicrobial prescription and safety of patients, subsequently limiting the emergence and spread of resistant bacteria.

1.4 RESEARCH QUESTION AND HYPOTHESES

This study was set to answer the question “What is the effect of performing the ASP’s strategies on reducing the spread of antimicrobial resistant bacteria in patients admitted to the ICU of South African hospitals?”

The null hypothesis states that promoting the quality of antimicrobial prescribing through ASP does not reduce the spread of antimicrobial resistant bacteria in the ICU of South African hospitals.

1.5 AIMS OF THE STUDY

1.5.1 PURPOSE OF THE STUDY

This study provides a comprehensive evaluation of whether the effectiveness of antimicrobial stewardship programme implemented in Gauteng academic hospitals in South Africa, achieved its objective of improving the quality of antimicrobial use, with the consequence of limiting the spread of resistant bacteria. The deficiencies in ASPs were identified and recommendations were made to achieve optimal performance.

1.5.2 OBJECTIVES OF THE STUDY

The objectives of this study were to:

- Determine the capacity of the hospital to appropriately prescribe antimicrobials.
- Determine the appropriateness of prescribing antimicrobials to patients suspected of having hospital-acquired infection after 48 -72h of admission.
- Determine the incidence of the variety of bacteria and their antimicrobial susceptibility patterns in patients admitted in the ICU.
- Assess the effectiveness of antimicrobial stewardship in improving the quality of antimicrobial prescribing in the ICU using the RE-AIM framework.
- Develop and recommend strategies for the improvement of antimicrobial stewardship programmes in the ICU.

1.6 SIGNIFICANCE OF THE STUDY

The significance of this study was informed by the ever-growing threat of antimicrobial resistance caused by use and misuse of antimicrobials in healthcare institutes. Promoting appropriate use of antibiotics through various interventions will help stop unnecessary prescribing and misuse of antibiotics. The findings of this research study will contribute substantially in strengthening infection control practices and preventing the emergence and spread of antimicrobial resistance in hospitals.

At a national level, the information provided in this study may inform policy decisions, such as antibiotic guideline development or revision, and help in prioritising public health action, such as education campaigns and/or regulatory measures. This information may also help address the problem of increasing rates of antimicrobial resistance in South Africa, which has dire consequences of prescribing expensive and /or more toxic antimicrobials as well as increasing the risk of patients developing resistant infections. Economically resistant infections not only cost more but can prolong the hospital stay increasing healthcare cost.

1.7 DEFINITIONS OF TERMS

1.7.1 Healthcare-associated infection

Health care-associated infection refers to a localized or systemic condition resulting from an adverse reaction to the presence of an infectious agent(s) or its toxin(s) that occurs in a patient in a healthcare setting, was not found to be present or incubating at the time of admission unless the infection was related to a previous admission to the same setting (McKibben, Horan, Tokars, Fowler, Cardo, Pearson, Brennan, & the Healthcare Infection Control Practices Advisory Committee 2005: 225)

1.7.2 Antimicrobial (AM)

Antimicrobials are naturally occurring or synthetic chemical agents that kill or inhibit the growth of microorganisms (Premanandh, Samara & Mazen 2016:1).

1.7.3 Antimicrobial stewardship (AMS)

Antimicrobial stewardship is defined as a multi-disciplinary, systematic approach to optimising the appropriate use of all antimicrobials to improve patient outcomes and limit the emergence of resistant pathogens whilst ensuring patient safety (Dellit et al. 2007:159).

1.7.4 Antimicrobial stewardship program (ASP)

Antimicrobial stewardship program is defined as an ongoing effort by a health care institution to optimize antimicrobial use among hospitalized patients in order to improve patient outcomes, ensure cost-effective therapy, and reduce adverse effects of antimicrobial use (MacDougall & Polk 2005: 640).

1.7.5 Antimicrobial resistance (AMR)

Antimicrobial resistance is the ability of a microorganism to survive and reproduce in the presence of antibiotic doses that were previously thought effective against them (Singh, Arora, Thangaraju, Singh & Natt 2013: 95)

1.7.6 Multi-drug resistance (MDR)

Multiple drug resistance is defined as resistance to two or more drugs or drug classes (Singh et al. 2013: 95)

1.7.7 Adverse effects

An adverse event is an untoward medical experience in a patient who has been administered a medication, and that event does not necessarily have to have a casual relationship with the treatment. The administration of a particular drug may results in prolonged hospital stay, cause a permanent disability, or death (Martin, Micek, & Wood 2010:155).

1.7.8 Prudent use

It means an educated appropriate prescription, using antimicrobials only in cases in which their administration was fully justified on objective grounds (Baquero & Garau 2010:487).

1.7.9 Surgical prophylaxis

It is defined as any dose of an antimicrobial agent given within 24 hour period before 8:00 am on the day of the survey (Sinatra, Carubia, Marchese, Aprea, Alessandro, Mammina & Toregrosa 2013: 201).

1.8.0 Medical prophylaxis

An antimicrobial therapy administered to prevent disease or its recurrence (Sinatra et al. 2013: 201).

1.8 RESEARCH DESIGN

A prospective, quasi-experimental descriptive survey was conducted to achieve the objectives of this study.

1.9 METHODOLOGY

Data collection occurred between July 2017 and September 2017 at large academic hospital in Gauteng, South Africa. The targeted participants were critically-ill elderly patients admitted in the intensive care unit. Data were extracted from patients' medical records using a structured questionnaire.

A detailed outline of research design and methodology will be given in chapter 3.

1.10 SCOPE OF THE STUDY

This study focused on the antimicrobial stewardship program, examining the program's performance in promoting appropriate antimicrobial prescribing in intensive care units in academic Hospital in Gauteng province, South Africa. Further, this study examined the effectiveness of the program in reducing the emergence of antimicrobial resistance.

1.11 LIMITATIONS OF THE STUDY

Since this was conducted in a natural setting involving critically ill patients it was difficult to select a control or treatment group, as such the limitations in this study included the lack of randomization for group assignments. Additionally, information was collected from adult patients only who were admitted to a general ICU, and as such, results were not generalizable to paediatric patients or other ICUs such as Burn unit.

While public healthcare facilities can provide valuable information on the impact of ASP, the exclusion of private healthcare sector from the study restricted the study from obtaining a comprehensive picture of the impact of ASP in South African hospitals.

1.12 STRUCTURE OF THE THESIS

The thesis is composed of five chapters, each chapter deals with a different aspect of the study.

Chapter one describes the aims and objectives of the thesis and also provides the rationale supporting the methodological approach to evaluating the impact of ASP. It gives both an overview and serves as an introduction to the study, establishing the background of the problem. Additionally, the chapter highlights the importance of evaluating the effectiveness of the program as well as defining basic terminology used in the thesis.

Chapter two presents the results of a broad literature review conducted prior to the start of this study, which was also used to inform the direction of this study. It touches on the work done by other researchers on the topics on antimicrobial stewardship and the spread of resistance demonstrating the gaps that the proposed research will fill.

Chapter three detail out the research methodology for the present study. It describes the pilot study, participants of the study, instrumentation done for the study, data collection and data analysis procedures of the study

Chapter four outlines the results of the study in relation to the research aims and objectives of the study. A detailed discussion on the significance of the results as well as the explanation for unexpected results is provided here.

Chapter five summarizes the thesis, provides the literature, methodology, and discussion of the main findings. The most significant results are emphasized.

Chapter six discusses the effectiveness of the ASP implemented in the hospital. It deals with the identified weakness of the program, to inform decisions on how to remedy the deficiencies identified. Additionally, this chapter discusses strategies proposed for the optimisation of the program.

Chapter seven discusses the strength and limitations of the study, also suggestions for further research as well as recommendations are presented herein.

1.13 CONCLUSION

The inappropriate use of antimicrobials causes harm to human health by introducing adverse drug effects and promotion of the development of antimicrobial resistance. Therefore, the gradual increase in antimicrobial-resistant pathogens in South Africa is of a great concern. This study aims to assess the impact of antimicrobial stewardship program (ASP) in limiting the spread of antimicrobial resistance in South African hospital. Thus, elucidating the weakness of the program with the aim of improving the quality of antimicrobial use. Guided by the RE-AIM framework, comprehensive evaluation of the effectiveness of the ASP on the promotion of the appropriate use of antibiotics was performed, and the areas that needed improving were highlighted to optimise the appropriate use of antibiotics.

CHAPTER 2

LITERATURE REVIEW

2.1 INTRODUCTION

This chapter provides an analysis of published literature that pertains to the effectiveness of antimicrobial stewardship on promoting the appropriate use of antimicrobials. It examines the causes and effects of antimicrobial resistance and the impact of ASP which aims to limit the spread of antimicrobial resistance. The main purpose of the literature review is to review previous studies on the implementation and impact of ASP as well as its effect on limiting adverse drug effects on hospital admitted patients. The theoretical basis of the main focus of the study is introduced and a detailed context of the literature review is provided.

2.2. SEARCH STRATEGY

The literature review was based on South African and international resources, with a focus on the scourge of antimicrobial resistance and the effects of antimicrobial stewardship. Various data search engines such as Google Scholar, Cochran database of systematic review and Pubmed, were utilised to obtain the materials for the literature review. The topic and the aims of the study were used as the basis for the subheadings of the literature review.

Search terms used for the literature included, antimicrobial management, antimicrobial stewardship, antimicrobial resistance, appropriate antimicrobial use, judicial antimicrobial use, acquisition of antimicrobial resistance, factors promoting antimicrobial resistance, hospital-acquired infections, nosocomial infections. Manual search of local conferences, theses, and dissertations to identify relevant articles was also performed. Additional sources including South African National Department of Health (NDoH), South African Antimicrobial Stewardship Program (SAASP), Centre for Disease Prevention and Control (CDC) and World Health Organization (WHO) as well as reference list of relevant articles, book chapters and reviews were also searched.

The literature search was restricted to English language publications. The review included studies that considered the implementation and the effectiveness of antimicrobial stewardship interventions in hospitals.

2.3 PATHOLOGY AND TREATMENT OF INFECTIONS

Infectious diseases currently cause about one-third of all human deaths in the world (Alberta, Johnson, Lewis, Raff, Roberts & Walter, 2002: 1485). In order to understand how the bacteria spread and become a burden to human health, the knowledge of colonization and invasion of the host by bacteria will be discussed in subsequent sections.

2.3.1 Bacterial mechanisms for invading the host

Microbes are ubiquitous in nature and humans are constantly exposed to them, some are harmless but may cause infectious diseases leading to acute or chronic illness (Albiger, Dahlberg, Henriques-Normark & Normak 2007:511). Only a marginal bacterial species have the ability to cause disease in humans (Alberta et al 2002:1490). Some bacteria have evolving mechanisms that aids them to successfully colonize and survive within the human body (Stones & Krachler, 2015: 2626). But their localization in the human body is normally restricted to certain areas of the body including: the skin, respiratory and gastrointestinal tracts (Alberta et al. 2002: 1501; Ribert & Cossart 2015: 173).

Opportunistic pathogens take advantage of injuries or breaches to penetrate the host barriers (Ribet & Cossart 2015: 173). Whereas, some bacteria produce proteases and directly target host mucins, which plays a role in limiting the microbial invasion of the microflora to reach the epithelial layer (Ribet & Cossart 2015: 174). Since microbiota play an important role in aiding host barriers against invading pathogens by competing for nutrients and niches with pathogens, and enhancement of host defence mechanism (Kamada, Chen, Inohara & Nunez 2014: 686- 687), the pathogens may involve triggering mucosal inflammation to alter the composition of the microbiota, to escape the host barriers. Subsequently increasing mucosal antimicrobial peptides to which pathogens may be resistant to, compared to the resident bacteria (Ribet & Cossart 2015: 175).

A variety of bacterial pathogens have acquired the ability to survive and replicate within macrophages after they have been taken up into a cell by phagocytes or receptor-mediated endocytosis (Alberta 2002: 1507; Chiang, Uzoma, Moore, Gilbert, Duplantier & Panchal 2018: 2). This mechanism protects the pathogen from the complement or adaptive immune system and helps the pathogen avoid competing with other resident microbes (Chiang et al 2018: 2).

According to Stones and Krachler (2015:2626) different bacterial species display a wide array of specialized cell surface organelles or macromolecules (pili or fimbriae) which aid in mediating attachment to target host structures for the colonization and penetration of the host. They adhere to the host by either using adhesions or through a non-specific adherence mechanism such as electrostatic forces and lipophilic/ hydrophobic interaction (Adlerberth, Cerquetti, Poillane, Wold & Collignon 2000: 225). These macromolecules help to overcome peristalsis in the gut and the flushing action of mucus, saliva, and urine, which remove non-adherent bacteria (Alberta et al. 1502- 1503). The pathogen that manages to survive the immune onslaught and penetrates host cells and the mucosal layer can exert their pathogenic effect and therefore replicate further.

2.3.2 Antimicrobial treatment of bacterial infections

According to Varley, Sule, and Absolom (2009: 184) throughout history, infectious diseases have been treated with a variety of herbal remedies; and the first true antimicrobial agent in the world was salvarsan, used for the treatment of syphilis and was discovered in 1909 by Paul Ehrlich (Varley et al. 2009:184; Saga & Yamaguchi 2009:104). Saga and Yamguchi (2009: 104) state that the originally discovered drugs were synthetic compounds and had limitations in terms of safety and efficacy, and in 1928, Fleming discovered a safe and efficient antibiotic, the penicillin.

Subsequently, new classes of antimicrobial agents were developed leading to a surge of the discovery of antimicrobial therapy (Saga & Yamguchi 2009: 104). Since then, the development of antimicrobials has greatly reduced mortality and morbidity from infectious diseases (Song 2003: 1). Because of antimicrobials development, millions of lives have been saved and important medical procedures including surgery and cancer chemotherapy enabled (WHO 2017:12).

2.4 THE DEVELOPMENT OF ANTIMICROBIAL RESISTANCE

Since their conception antimicrobial agents have been used to treat infectious disease and have been successful in reducing illness and death from infectious microbial species (Baker, Thomson, Weill & Holt 2017: 733; Brinkac, Veerhies, Gomez & Nelson 2017: 1002;Premanandh, Samara & Mazen 2016: 1). Lately, the effectiveness of the agents has declined, whereas, the frequency of antimicrobial resistant pathogens have increased (Michael, Dominey-Howes, Labbate 2014:1; Palmer & Kishony 2013: 243). In addition, the development of novel antimicrobial agents has dramatically declined (Spellberg, Powers, Brass, Miller & Edwards, Jr. 2004: 1279-1280). The situation is exacerbated by the rapid development of antimicrobial resistance, which renders the existing microbial agents obsolete (Perron, Inglis, Pennings & Cobey 2015: 211). Such occurrence puts a strain in the effective treatment of common nosocomial infection leading to a significant deterioration of clinical outcome (Dik, Poelman, Friedrich, Ronday, Lo-Ten-Foe, van Assen, van Gemert-Pijnen, Niesters, Hendrix & Sinha 2015: 93).

Hospitals are an important breeding ground for the development and spread of antimicrobial resistant bacteria (Struelens 1998: 652). Infections acquired in the hospital (HAIs) are a cause of significant morbidity and mortality, worsened by the development of antimicrobial resistant infections in patients receiving health care (Brink, Feldmann, Duse, Gopolan, Grolman, Mer, Naicker, Paget, Perovic & Richards 2006: 153; Struelens 1998: 652). The Centres for Disease Control and Prevention (CDC) define HAI as a localized or systemic condition resulting from an adverse reaction to the presence of an infectious agent(s) or its toxin(s) that develop during hospitalization, with no evidence that the infection was present or incubating at the time of admission to the acute care setting (Horan & Gaynes 2008: 309). WHO (2002: 1) emphasizes that a patient must be admitted for a reason other than the developed infection.

Weinstein (1998: 417) points out that HAI typically affects patients, who are immunocompromised because of age, underlying diseases, or medical or surgical treatment. As a consequence to the patients' frail conditions, exposure to heavy antimicrobial use, overcrowded and poor ventilated wards, surgical procedures, and daily invasive procedures, patients admitted to ICUs are the most susceptible to

nosocomial infections (Baker et al 2017: 735; Valles, Leon & Alvarez-Lerna 1997:387). Furthermore, patients who are treated with inadequate antibiotic therapy are at risk of a poor outcome and are a high risk of spreading the resistant pathogen further (Acar, 1997: 17). Moreover, inadequate antibiotics therapy originate from inappropriate interpretation or use of microbiological test results; lack of microbiologically confirmed diagnosis; laboratory test errors; failure to submit appropriate specimen for culture; misuse of microbiology resources (Moreney-Patvin, Schwartz & Weinstein 2017: 382).

The agents of utmost importance in HAI include *Streptococcus* spp., *Acinetobacter* spp., enterococci, *Pseudomonas aeruginosa* (*P. aeruginosa*), coagulase-negative staphylococci, *Staphylococcus aureus* (*S. aureus*), *Enterobacteriaceae, K. pneumonia* (*Klebsiella pneumonia*), *Escherichia coli* (*E. coli*) (Babamahmoodi, Ahangarkani & Davoudi 2015: 153; WHO 2002: 2). A retrospective descriptive study from Kimberly hospital Burn Unit, showed *Staphylococcus aureus*, coagulase-negative *Staphylococcus* (CNS) and methicillin-resistant *S. aureus* (MRSA) as the most common pathogens isolated (40.17%) on wound swabs, whereas in blood cultures *S. aureus* (32.08%), *K. Pneumonia* (20.75%) and *P. aeruginosa* (16.98%) were the most frequent pathogens found (Giaquinto-Cilliers, Hoosen, Govender & van der Merwe 2014: 30).

Owing to the increased incidence of HAI with antibiotic-resistant bacteria, antibiotic resistance has become a critical challenge for infective disease management. More than 70% of the bacteria that causes HAIs are resistant to at least one antibiotic (Krzowska-Firych, Kozlowska, Sukhadia & Al-Mosawi 2014: 784). Lately antimicrobial resistance (AMR) is recognized globally as one of the greatest threats to human health (Llor & Bjerrum 2014: 229), and further, microbes have developed resistance to the majority of available antimicrobials (Laxminarayan, Duse, Wattal, Zaidi, Wertheim, Sumpradit, Vlieghe, Hara, Gould, Goossens, Greko, So, Bigdeli, Tomson, Woodhouse, Ombaka, Peralta, Qamar, Mir, Kariuki, Bhutta, Coates, Bergstrom, Wright, Brown & Cars 2013:1057), consequently complicating the management of infectious diseases.

In addition to antibiotic resistance impacting negatively on the ability to effectively manage infectious diseases, antimicrobial resistance results in increased morbidity, mortality and economic expenditure (Borg 2009: 7; Ozer, Tatman-Otkun, Memis & Otkun 2010: 203- 204). To improve on the impact of antimicrobials, the defence mechanisms of bacteria from antimicrobials' assault should be understood.

2.5 MECHANISMS OF ANTIMICROBIAL RESISTANCE

Antimicrobial agents exert their activities selectively on vital microbial functions with minimal effects on or without affecting host functions (Lakshmi, Nusrin, Ann & Sreelakshmi 2014: 37; Toma & Dyeno 2015: 29). The antimicrobials act by targeting specific sites of microbes to retard their proliferation through the inhibition of bacterial cell wall synthesis, protein synthesis, folic acid synthesis, and/or DNA replication (Liwa & Jaka 2015: 877; Toma et al. 2015:29).

However, microbes have developed a variety of mechanisms to protect themselves against the effects of antimicrobials (Hawkey 1998: 657; Brinkac et al 2017: 1002). These mechanisms may be intrinsic or acquired by mutation or horizontal transfer of genes or DNA containing resistance determinants (Holmes, Moore, Sundsfjard, Steinbakk, Regmi, Korkey, Guerin & Piddock 2015:3; Kumar & Varela 2013: 523; Liwa & Jaka, 2015: 879-880). In intrinsic resistance, bacteria may comprise bacterial chromosomal DNA containing genes for antibiotic resistance. Additionally, microbes may either lack target sites for the antimicrobials or have low permeability to those agents that require entry into the microbial cell in order to effect their action (Toma & Dyeno 2015: 30). A common example of intrinsic resistance is demonstrated in the bacteria-impermeable to antimicrobials which prevent antimicrobial's access to target sites. This is observed in enterococcus spp. and *Pseudomonas aeroginosa* (Kapil 2005:84; van Hoek, Mevius, Guerra, Mullany, Roberts & Aarts 2011:1).

Regarding acquired antimicrobial resistance, bacteria exposed to a specific evolutionary pressure e.g. antimicrobials may develop a defence mechanism against that antimicrobial or class of antimicrobials (Toma & Dyeno 2015: 30). Bacteria may contain genetic material that can spread from one bacterium to another through plasmids, bacteriophages, and transposons or integrons (Hawkey 1998: 659; Martin et al. 2010: 155; Perron, Inglis, Pennings & Cobey 2015: 214). Fundamentally,

antibiotic resistance can be acquired through sharing and transfer of genetic materials by 1) conjugation which involves cell-to-cell contact for the transfer of extra-chromosomal, 2) transduction which involves the infection of bacteria by viruses, passing along genes from one infected organism to the next (bacteriophage), and 3) transformation whereby naked DNA is acquired from the environment having been released from another cell (Barbosa & Levy 2000:305).

Bacteria can also adapt to antimicrobial assault using a wide variety of mechanisms (van Hoek et al. 2011: 1). The bacteria can protect themselves from antibiotics through active efflux that drives out antibacterial compounds from the bacterial cell thus reducing their intracellular concentrations to sub-or non-inhibitory levels (Kumar & Varela 2013:525). This mechanism is demonstrated in the efflux of the tetracycline antibiotics through an export protein from the major facilitator superfamily (MFS) (Byarugaba 2010: 21).

In addition, bacteria can inactivate antibiotic agents through the production of enzymes that degrade or modify the drug itself through either hydrolysis group transfer and/or redox mechanisms (Dzidic, Suskovic & Kos 2008: 13; Hawkey 1998:657- 658). For example, inactivation of the drugs by aminoglycoside-modifying enzymes, using the enzymes, acetyltransferases (AAC), nucleotidyltransferases or adenyltransferases (ANT), phosphotransferase (APH) to render antimicrobials inactive (van Hoek et al. 2011:2). Additionally, the bacteria can protect themselves from antibiotic agents by modification of antibiotic targets whereby the target site is modified so that the antibiotic is unable to bind properly (Dzidic et al. 2008: 13). For example, methicillin-resistant *S. aureus* with altered penicillin-binding proteins (Kapil 2005: 84).

A study of van de Sande-Bruinsma, Grundmann, Verloo, Tiemersma, Monen, Goossens, Ferech, and the EARSS and ESACPG (2008:1727) found that an association between antimicrobial drug use and resistance exist and was specific and robust for 2 of the 3 compound combinations under study. The authors concluded that the data suggest that in Europe the variation of consumption coincides with the occurrence of resistance at country level (van de Sande-Bruinsma et al. 2008:1726). The authors further suggested that the mechanisms for acquiring

resistance against both substances involved successive alterations of chromosomally located genes by either homologous recombination or point mutations, resulting in a stepwise modification of the molecular targets (van de Sande-Bruinsma et al. 2008:1727). This study demonstrates a relationship between antimicrobial use and the development of antimicrobial resistance.

In light of the processes discussed above, acquisition of resistance may increase the survival rate and spread of bacteria under the assault of antibiotics. Consequentially the acquired resistance limits the choice of antibiotics that can be used for treatment. According to Barbosa and Levy (2000: 306), current major problems of antibiotic resistance are seen in methicillin-resistant *S. aureus* (MRSA), penicillin-resistant *S. pneumoniae* (PRSP), multidrug-resistant *M. tuberculosis* and vancomycin-resistant enterococci (VRE). Recently, a plasmid-borne colistin resistance gene, *mcr-1* in a cultured *E.coli* strain was found in a patient with a urinary tract infection (UTI) in the United States (McGann, Snesrud, Maybank, Corey, Ong, Clifford, Hinkle, Whitman, Lesho & Schraecher 2016: 4420).

Therapeutic options for several highly resistant gram-negative pathogens such as *Acinetobacter* species, multidrug-resistant (MDR) *P. aeruginosa,* and carbapenem-resistant *Klebsiella* species and *Escherichia coli*, are so extremely limited that clinicians are forced to use older drugs that are associated with significant toxicity (Boucher, Talbot, Bradley, Edwards, Gilbert, Rice, Scheld, Spellberg & Bartlett 2009: 2). The number of antimicrobials in phase 2 or 3 of clinical development remains disappointing. In addition, the numbers of new antimicrobials that receive FDA approval has decreased (Boucher et al. 2009:7-8). Therefore, to devise an effective strategy for addressing the problem of antibiotic resistance requires an understanding of the basis of the factors contributing to inappropriate antimicrobial use and or prescribing (Oxford, Goossens, Schedler, Sefton, Sessa & van der Velden 2013: 291).

A review aimed at understanding and describing the current status of antimicrobial resistance in Africa in relation to common causes of infections and drugs recommended in WHO treatment guide found that Gram-negative pathogens reported were *E coli* (87/144: 60.4%), (Tadesse, Ashley, Ongarello, Havumaki,

Wjegoonewardena, Gonzalez & Dittrich 2017:619). In the gram- positive pathogens, Coagulase negative Staphylococcus species such as *S aureus, Streptococcus pneumonia* and group A streptococcus were the most commonly reported bacteria (Tadesse, et al 2017:619). The review identified a high level of resistance of Enterobacteriaceae to ampicillin and co-trimoxazole, as well as high resistance to co-trimoxazole and tetracycline by *S pnuemoniae* were reported indicating a rising pattern in AMR in certain pathogens (Tadesse, et al 2017:632).

In South Africa, an increase in antimicrobial resistance in all major types of pathogenic bacteria was observed, and that there are no antimicrobials in the pipeline or expected in the near future for the treatment of Gram-negative bacteria, the cause of common infections (NDoH 2015:9). In addition, an increase in the burden of antimicrobial resistance was observed from 2010, this included the realisation that one half of all hospital-acquired *S aureus* in public hospitals were resistant to methicillin; an outbreak of vancomycin-resistant enterococci; and the production of extended-spectrum beta-lactamase (ESBL) by common Gram-negative bacteria such as *K pneumonia* and *E coli* rendering them resistant to penicillins and cephalosporins (NDoH 2015: 9 -10).

2.6 BARRIERS TO APPROPRIATE ANTIMICROBIAL PRESCRIBING

To curb the growing burden of antimicrobial resistance, and optimize antimicrobial prescribing behaviours as well as promote quality improvement, policies and evidence-based interventions were drafted and implemented by the governments and healthcare institutions, (Charani, Castro-Sanchez, Sevdalis, Kyratsis, Drumright, Shah & Holmes 2013: 188). In an effort to curb antimicrobial resistance and promote quality improvement of antimicrobial prescriptions, South African Antimicrobial Stewardship Program (SAASP) was formed (NDoH 2015: 10). The SAASP promoted appropriate antimicrobial prescribing by availing an antimicrobial prescription chart on the SAASP website, as well as introducing the national guidance for the use of antimicrobials at different levels of institutions and district in the essential drug list (EDL) and standard treatment guidelines (STGs) (NDoH 2015: 10 – 12).

Although healthcare providers are aware of problems associated with inappropriate prescribing, they often prescribe antibiotics against their better judgment (Oxford et al. 2013: 291-292). A study by Adorka, Dikokole, Mitonga and Allen (2013: 349), found that healthcare providers are influenced by patients' requests and expectations in prescribing antibiotics, even if an infection has been ruled out, and/or the diagnosis is not clear. Whereas, a study by Chaves, Cheng, Runnegar, Kirschner, Lee & Buising (2014: 570), showed that consultants, residents, and interns are also influenced by senior doctors who are more knowledgeable in prescribing antibiotics.

In addition, a number of factors that influence the ability of healthcare providers to prescribe antimicrobial were identified (Livorsi, Comer, Matthias, Perencevich & Bair 2015: 1066). These included: 1) uncertainty in diagnostic, which leads to healthcare providers prescribing broad-spectrum therapy in fear of missing and an undetected infection. 2) fear of lawsuits, wherein, healthcare providers will initiate antibiotics therapy even in patients without a definitive infection; 3) being more concerned with achieving a clinical cure for a suspected or proven infection than preventing potential adverse effects of antibiotics: 4) respect of hierarchy whereby, healthcare providers fear to critique each other even when antibiotics are prescribed unnecessarily (Livorsi et al. 2015:1068)

There are considerable variations seen in adherence to antibiotic prescribing guidelines across healthcare providers. The study of Skodvin, Aase, Charani, Holmes and Smith (2016: 30), demonstrated that interns and inexperienced residents regard National guideline as a useful tool. While the more experienced residents use the guideline as a reference for checking dosages and treating uncommon infectious diseases (Skodvin et al. 2016: 29). Furthermore, the lack of adherence to the guideline among senior doctors could be explained by time consumption due to suboptimal IT-systems (Skodvin et al. 2016: 29). Whereas, another study identified a gap in knowledge of antimicrobial prescribing, noncompliance to local and hospital guidelines, reliance on senior colleagues to make antimicrobial prescribing decisions were as barriers to appropriate antibiotic prescribing was also identified (Chaves et al. 2014: 570, 572).

In addition to misuse of antibiotics by both patients and healthcare providers (Barbosa & Levy, 2000: 304; Planta 2007:534; Sande-Bruinsma et al. 2008: 1727), antibiotic resistance risk factors are also associated with the change of preference of antimicrobial agents by the clinician (Boonsong, Chongtrakool, Srisangkaew & Santanirand 2011: 244); fear of bad outcomes, lack of access to quality laboratory services, lack of healthcare providers' knowledge regarding optimal diagnostic approaches as well as diagnostic uncertainty and habitual prescribing (Adorka , et al. 2013. 344; Om, Daily, Vlieghe, McLaughlin & McLaw 2006:64; Oxford et al. 2013: 291- 292). Moreover, Adorka, Allen, Lubbe & Serfontein (2013: 134:137), noted that the severity of the infections encountered complicates and provides a challenge for the health providers to use their knowledge in the treatment of infections.

Confirmation of the infection and the Identification of the responsible pathogen from biological samples obtained from the patients, is crucial before initiating the therapy to be able to select the appropriate treatment, and facilitate therapy de-escalation in response to susceptibility profiles (Luyt, Brechot, Trouillet & Chastre 2014: 481). Pulcini and Gyssens (2013: 194) concur by suggesting that the empirical therapy should be decided upon at local level, guided by local antibiograms and patient outcome data. The lack of antibiograms and comprehensive antibiotic prescribing guidelines, compel the healthcare providers to take the responsibility of prescribing antibiotics based on their knowledge and experience (Adorka et al. 2013: 345).

In Cambodia, antibiotic prescribing generally occurs in the absence of microbiological evidence of infection regardless of accessibility to microbiological services. Furthermore, the empirical treatment is changed to a broader spectrum antibiotic without microbiological evidence (Om et al. 2006: 61). The lack of availability of microbiological specimen and timeliness of the results has been shown to pose a major challenge in prescribing antibiotics (Skodvin et al. 2016: 26). Whereas, in hospitals lacking microbiological laboratory, the prolonged broad-spectrum antimicrobial treatment is attributed to the delay of specimen transport and transfer of results into separate electronic systems (Skodvin et al. 2016: 26).

As highlighted above, healthcare providers lack consistency in the capacity to prescribe and in the use of practical educational resources, they lack communication

skills, do not adhere to national and local guidelines. Therefore, informing and educating healthcare providers on appropriate prescribing may reduce the adverse effects due to antimicrobials.

2.7THE BURDEN OF ANTIMICROBIAL RESISTANCE

To capture the number of deaths attributable to the failure of antibiotic therapy due to antibiotic resistance, the term ‘burden of antibiotic resistance' is used and can be estimated by the frequency and clinical impact of failures of antibiotic therapy (Woolhouse, Wough, Perry & Nair 2016:1). The burden of antimicrobial resistance in the United States of America is estimated at 23 000 patients' death per year (CDC 2013: 17). Whereas, in Europe, 25 000 fatalities were estimated for each year (ECDC 2011: 15). Reported data suggests that almost 19 000 patients die per year in Thailand (Lim, Takahashi, Hongsuwan, Wuthiekanun, Thamlikitkul, Hinjoy, Day, Peacock & Limmathurotsakul 2016:18082).

The unsuccessful surveillance programmes, insufficient data and a lack of research in the field makes the situation of antimicrobial resistance in sub-Saharan Africa unclear (Mendelson & Matsoso 2015:325). A systematic review of 8 studies published between 2000 and 2011 conducted in South Africa found that there was no national surveillance system that collates and collects data year on year to assess trends and resistance patterns for nosocomial pathogens (Nyasulu et al. 2012: 12).

In an editorial section of GARP situational analysis part 2, Duse (2011: 551) acknowledged a major shortcoming of the AMR surveillance in the public healthcare sector. The authors point out that the approach used provides data collected only from large academic centres and does not profile AMR in the general population attending primary, secondary and non-academic tertiary health care facilities do not reflect the extent of AMR countrywide (Duse 2011: 551).

Moreover, the burden of antibiotic resistance on health in South Africa is not unknown (Cosgrove & Carmelli 2003: 1433; Truter 2015: 52). Even so, antimicrobial resistance, HIV/AIDS, tuberculosis (TB) and malaria are major contributors to the high burden of infectious diseases (Crowther-Gibson, Govender, Lewis, Bamford, Brink, Gottenberg, Klugman, du Plessis, Fali, Harris, Keddy & Botha 2011:569). A

growing evidence of escalating rates of antimicrobial resistance to several conventional antimicrobials was demonstrated in the studies reviewed by Nyasulu et al. (2012: 12).

The worldwide estimates of the burden of antimicrobial resistance demonstrate that the emergence and spread of antimicrobial resistance have exacerbated the battle against infectious disease. In addition, this occurrence continues to contribute substantially to the death toll caused by AMR. Therefore, the reported estimates provide compelling evidence of the need for strategies to prevent and control this afflicts.

Furthermore, it has been highlighted that the limited access and delays in access to antibiotics plays an important role in the high death rate observed in people with infections compared to antimicrobial resistance, however access to antibiotics is still a challenge (Laxminarayan, Matsoso, Pant, Brower, Rettingen, Klugman & Davies 2016: 169). Mendelson, Rettingen, Gopinathan, Hamer, Wertheim, Bosnyot, Butler, Tomson and Balasegaran (2016:188) points out that unrestricted access to antibiotics has the potential to substantially reduce morbidity and mortality in patients with infections, especially when unrestricted access is paired with appropriate use of antibiotics.

2.8 ANTIMICROBIAL STRATEGIES IN GENERAL

Various organizations and policy makers concur that inappropriate use of antimicrobials provide selective pressure for the development and spread of AMR (De Angelis, Restuccia, Cauda, Tacconelli 2011: 377; Levy 2001:124). The degree of the scourge of AMR prompted the World Health Organization calling for urgent intervention (WHO 2012: 2). Furthermore, Levy (2001:125) point out that a great impact on resistance can be achieved by changing the practice of inappropriate prescribing of antibiotics. Accordingly, antimicrobial stewardship programs (ASPs) use a variety of strategies and techniques to optimize antimicrobial use in hospitals (Doron & Davidson 2011:1115). The primary objectives of an ASP are to ensure effective treatment of patients with infections while minimizing unintended consequences of antimicrobial use (Dellit et al. 2007: 159). These objectives can be

achieved through the formulation of policies, use of treatment guidelines, surveillance data, education resources, targeted interventions and audit (Dellit et al. 2007: 159).

According to Njoku and Hermsen (2010: 51), antimicrobial stewardship is a patient safety measure that is multifaceted in nature and requires a collaborative, multidisciplinary approach to be successful. A collaboration of personnel with the appropriate qualifications such as pharmacists with infectious diseases training; infectious diseases physicians to help with antimicrobial stewardship; informatics personnel to maintain databases, as well as infection control (IC) and epidemiology departments are essential for the ASP to be a success (Dellit et al. 2007: 160; Kolman, Geertsema, van den Berg & Goff 2016: 25; Njoku & Hermsen 2010: 55).

Different interventions have been proposed by the Infectious Disease Society of America and Society for Healthcare Epidemiology of America, to offer a guide in appropriate and cost-effective use of antibiotics in hospitals (Dellit et al. 2007: 159). The interventions included core strategies that provide the foundation of an ASP: the prospective audit with intervention and feedback, and formulary restriction with preauthorization, which may be supplemented by either guidelines and clinical pathways, dose optimization, education, protocols and antimicrobial order forms, surveillance and clinical decision support databases, streamlining and de-escalation, and intravenous (IV) to oral (PO) conversion strategies (Dellit et al. 2007: 159).

In the front-end or restrictive approach, the use of certain antibiotics based on the spectrum of activity, cost, or associated toxicities are restricted to ensure that use is reviewed with an antibiotic expert before therapy is initiated. Additionally, the front-end approach has the advantage of targeting specific antimicrobials for specific indications based on local resistance patterns and the hospital formulary (Doron & Davidson 2011: 1115).

Four distinct types of restrictive interventions have been identified (Davey, Brown, Charani, Fenelon, Goud, Holmes, Ramsay, Wiffen & Wilcox 2013: 7). These included: 1) Compulsory order form – which involves the completion of a form with clinical details to justify use of the restricted antibiotics; 2) Expert approval – whereby the prescription for a restricted antibiotic had to be approved by an Infection

specialist or by the Head of Department; 3) Restriction by removal – involves enforcing a restrictive policy in the target ward or unit, for example by removing restricted antibiotics from drug cupboards; 4) Review and make change – whereby the reviewer changes the prescription rather than giving health professionals either a verbal or written recommendation that they should change the prescription (Davey et al. 2013:7).

Nevertheless Njoku and Hermsen (2010: 55-56) noted that the use of antimicrobial restriction as a means of controlling antimicrobial resistance has limitations in the ICU setting. It is often associated with an increase in the use of alternative agents, and perceived loss of prescriber autonomy in that prior approval of the use of the restricted antimicrobials is required, consequently causing delays in initiating antimicrobial treatment to critically ill patients (Johnson & Banks 2017: 112; Njoku & Hermsen 2010:56).

Johnson and Banks (2017:112) recommend a ward-focused antimicrobial round, prospective audit and feedback strategy. In this strategy, current antibiotic prescriptions are reviewed and clinicians are provided with recommendations to continue, adjust, change, or discontinue the therapy based on the available microbiology results and clinical features of the case are provided (Doron & Davidson 2011: 1115; Johnson & Banks 2017: 112). The impact of the prospective audit and feedback strategy was demonstrated in the study by Newland, Stach, De Lurgio, Hedican, Yu, Herigon, Prasad, Jackson, Myers and Zaoutis (2012: 179). This study revealed a significant decrease in the use of antibiotics from 37% at the beginning of the program to 13% at the end of the program (Newland et al. 2012: 182). The study of Nilholm, Holmstrand, Ahl, Mansson,Odenholt, Tham, Melander and Resman (2015: 1) showed a significant reduction in antibiotic use due to an Infectious Disease specialist- guided, audit based ASP

The IDSA/SHEA guidelines (Dellit et al. 2007: 159) suggest that the ASM program should include one or both core strategies, and be complemented by either of the strategies mentioned above (Delitt et al. 2007: 160). Chang, Chen, Lin, Tang, Hsu, Weng, Lee, Wang and Lo (2017: 356) caution that an ASP that proved successful in one institute may be confronted with difficulties in another because of cultural

differences. Therefore, institutions should adopt the strategies that are more likely to succeed and the measures that are most cost-effective (Chang et al. 2017: 356). Furthermore, some protocols such as antibiotic cycling are difficult to implement and to comply with, because the optimal duration for cycling are not entirely clear (Cadena, Taboada, Burgess, Ma, Lewis II, Freytes & Patterson 2007:153).

In their study, Chang et al. 2017: 356) found a reduced consumption of total antibiotics and specific antimicrobial agents (imipenem, meropenem, and glycopeptides) within a short period using a focused educational program for primary prescribers. They also observed that antimicrobial prescribing can be optimized by the advancing their knowledge of general medicine, microbial virulence, immunological and genetic host factors, PK and PD properties of drugs, and basic knowledge of epidemiology (Chang et al., 2017: 356). The German Society for Infectious Diseases points out that education and training should be offered repeatedly as they are not sustainable as a one-off measure (de With, Allerberger, Amann, Apfalter, Brodt, Eckmanns, Fellhauer Geiss, Janata, Krause, Lemmen, Meyer, Mittermayer, Porsche, Presterl, Reuter, Sinha, B, Straub, Wechsler-Fordos, Wenisch & Kern 2016: 400).

The study of Baktygul, Marat, Ashirali, Harun-or-Rashid & Sakamoto (2011: 165), highlights the importance of the ASP and the adoption of international standard and local guidelines of antibiotic use in a hospital. The authors found a high level of inappropriate use of antibiotics in the hospital, and that parenteral administration of antibiotics (79.4%) was more common than oral (20.5%) (Baktygul et al. 2011: 165). The lack of clear guidelines in the hospital protocol for the choice of the route of treatment resulted in parenteral drugs not being switched to oral form (Baktygul et al. 2011:165). Moreover, the study showed that 73.3% of patients were inappropriately prescribed antibiotic therapy due to the lack of antibiotic prophylaxis and the long-term use of antimicrobials in the postoperative period (Baktygul et al. 2011: 165).

Although there are some countries that lack behind in implementing antimicrobial stewardship, most countries have observed the call to implement ASP in hospitals. A global cross-sectional survey conducted to investigate the depth and penetration of AMS across the world, showed that European hospitals had the longest running AMS

programmes and that 52% of the countries had national AMS standards, while 4% planned to introduce them (Howard, Pulcini, Hara, West, Gould, Harbarth & Nathwani 2015: 1246).

2.9 AMS STRATEGIES IN SOUTH AFRICA

In light of the current status of AMR in South Africa, a South African Antibiotic Stewardship Programme (SAASP) working group identified four priority interventions to effect change in the antibiotic prescribing practice (SAASP Working group 2012). These involved: 1) the appropriate use of microbiological diagnostic tests prior to initiation of antibiotics to allow de-escalation and rationalization of therapy; 2) decreasing the overall consumption of antibiotics in South Africa, recognizing that all antibiotic prescribing predisposes to emergence of multi-drug resistance (MDR); 3) decreasing the duration of antibiotic therapy, by setting clear evidence-based guidelines or where good evidence is not available, use expert opinion from within the SAASP working group to define optimal duration. Develop pharmacy systems to identify and block prolonged antibiotic duration as well as 4) addressing inappropriate dosing of antibiotics, with specific relation to use of loading doses and weight-based dosing where evidence exists, and directing the correct use of therapeutic drug monitoring (TDM) (SAASP Working group 2012).

In 2015, South Africa developed the National AMR Strategic framework to combat increasing levels of resistance in bacteria other than tuberculosis, and limit further increases in resistant microbial infections, and improve patient outcomes (NDoH 2015: 8). The framework defines the principles and short to medium term interventions needed to preserve the effectiveness of antimicrobials for future generations; to improve the appropriate use of antibiotics in human and animal health; to improve the effective management of antibiotic-resistant organisms and prevent their transmission further to create an enabling environment for the successful and sustainable implementation of the strategic objectives (NDoH 2015:10).

In 2017, guidelines on implementation of antimicrobial strategy in South Africa were published in accordance with the strategic framework and implementation plan

(NDoH, 2017: 8). The guide acts as an outline for the necessary steps to be taken by the South African healthcare providers to endorse AMS at national, provincial, district and health establishment levels (NDoH 2017: 8). In line with the recommendations of IDSA/SHEA guidelines, the practical guide recommends an AS team consisting of a prescriber, trained in antibiotic stewardship and a pharmacist who has either received stewardship training or to be trained as core members, supported by an IPC officer, microbiologist and/or intensivist and/or infectious diseases-trained specialist (NDoH 2017: 22).

A study by Boyles, Whitelaw, Bamford, Moodley, Bonorchis, Morris, Rawoot, Naicker, LusakiewiczI, Black, Stead, Lesosky, Raubenheimer, Dlamini and Mendelson (2013:4), endorsed the implementation of antibiotic prescription charts and the rollout of AS ward round activity in every healthcare institution, with the aim of reducing the volume of antibiotic use and slowing the evolution and spread of resistant bacterial strains. Antimicrobial stewardship ward rounds, a prospective audit and feedback intervention, involves reviewing prescriptions at ward level, providing feedback to relevant personnel, collecting data on compliance and antimicrobial consumption (Chung, Wu, Yeo, Chan & Hsu 2013: 152). Resulting in the optimization of the use of appropriately prescribed antibiotics for patients with proven or suspected bacterial infection; ensuring patient safety by stopping or suggesting alterations in prescribing when sub-optimal, and/or where infection prevention is not being correctly applied; to transfer AS skills to senior and junior doctors, nurses, pharmacists and IPC officers (Chung et al. 2013: 152 -153).

2.10 ASP IN THE ICU

Antimicrobial stewardship programs (ASP) were developed to determine the best approach to antimicrobial prescribing, decreasing costs of healthcare, improving patient outcomes and preventing further creation of antimicrobial resistance (Shlaes, Gerding, John, Craig, Bornstein, Duncan, Eckman, Farrer, Greene, Lorain, Levy, McGowan, Paul, Ruskin, Tenover & Watanakunakorn 1997:275). Key components of antibiotic stewardship in ICUs include rapid identification of patients with bacterial infections, better empirical treatment selection, using pharmacokinetic-pharmacodynamic (PK-PD) characteristics to optimize antibiotic dosing and administration modalities, de-escalation once culture results become available,

shortening therapy duration, and reducing the numbers of patients treated unnecessarily (Kollef, Sherman, Ward & Fraser, 1999: 472; Luyt, Brechot, Trouillet & Chastre 2014: 480).

An observational study using the multicenter database OUTCOMEREA, which contains data from 12 ICUs in France, found that ICU-acquired bloodstream infection (BSI) was associated with a 3-fold increase in the risk of hospital death (Garrouste-Orgeas, Timsit, Tafflet, Misset, Zahar, Soufir, Lazard, Jamali, Mourvillier, Cohen, De Lassence, Azoulay, Cheval, Descorps-Declere, Adrie, de Beauregard & Carlet 2006: 1123). The higher incidence is partly attributable to the high proportion of BSI cases due to *S. aureus* (20%) or coagulase negative staphylococci (21.5%) and to the high proportion of primary BSI (32%) (Garrouste-Orgeas et al. 2006: 1124). The results further showed a 6-fold increase in the risk of mortality associated with gram-negative bacilli, compared with the risk of mortality associated with gram-positive microorganisms (Garrouste-Orgeas et al. 2006:1124).

Furthermore, the study demonstrated that an interval of more than a day before initiation of appropriate antimicrobial therapy was associated with a 2-fold increase in the risk of death (Garrouste-Orgeas et al. 2006:1124). This study highlights the impact of ICU-acquired BSI on mortality among the exposed patients, the consequence of delaying a treatment in the ICU.

Generally in the ICU, an initial antibiotic therapy should be a broad-spectrum antibiotic therapy to avoid the detrimental consequences associated with inappropriate antibiotic therapy (Kollef et al.1999: 472: Luyt et al. 2014: 6). Although combination therapy is generally preferred in the empiric management of infection in critically ill patients, it has its disadvantages. Potential disadvantages of combination therapy include increased drug toxicity, the risk of infection with resistant pathogens and increased drug cost (Vincent, Bassetti, Francois, Karam, Chastre, Torres, Roberts, Taccone, Rello, Calandra, De Backer, Welte & Antonelli 2016:134). To avoid further development of resistant pathogens the antimicrobial regimen should subsequently be narrowed (de-escalated) or discontinued altogether based on the patient's clinical course and culture results (Kollef et al. 1999:472; Vincent et al. 2016: 135).

Joung, Lee, Moon, Cheong, Joo, Ha, Sohn, Chung, Suh, Chung, Song & Peck (2011:80) Define de-escalation as streamlined antibiotic treatment driven by microbiological documentation, clinical data and the severity-of-illness index achieved by decreasing the number and/or spectrum of antibiotics. In a retrospective, observational cohort study Joung et al. (2011: 85), found that the pneumonia-related mortality rate was not significantly different in the de-escalation group compared to the non-de-escalation group at day 14. The pneumonia-related mortality and overall mortality at day 30, however, was significantly lower in the de-escalation group. Furthermore, the study found that more than 40% of patients with negative cultures received de-escalation therapy, and all 12 patients survived at day 30 after the diagnosis of pneumonia but among all patients with negative cultures only two patients in the non-de-escalation group died (Joung et al. 2011: 85).

According to Cha, Michienzi & Hsaiky (2012:5) pharmacokinetic/ pharmacodynamic profiling is an invaluable approach in the design and application of antimicrobial dosing strategies to optimize clinical outcomes. Even-though inter- and intra-patient pharmacokinetic variability may render the design of dosing regimens difficult when treating patients in the ICU (Cha et al. 2012: 8). Therefore, for appropriate antimicrobial therapy, pathophysiological changes associated with critical illness that may alter the pharmacokinetics (PK) for example, increased the volume of distribution (Vd) and augmented clearance (CL) should be considered (Vitrat, Hautefeuille, Janssen, Bougon & Sirodot 2014: 264). In addition, strategies that may be considered for dose optimization include extended or continuous infusion of beta-lactams; once-daily dosing of aminoglycosides; appropriate dosing of antimicrobials (e.g. vancomycin, polymyxins, cefepime); weight-based dosing of certain antimicrobials dose adjustments for patients with renal dysfunction (MOHM, 2014: 23).

2.11 BARRIER TO IMPLEMENTATION OF ASP

Although ASPs have been shown to reduce inappropriate antimicrobial use with subsequent reductions in antimicrobial resistance, as discussed above, they are also confronted by barriers in their implementation. For example, inadequate infectious diseases expertise and resources have been identified as the main barriers to implementation of antimicrobial stewardship programmes in almost all public and

private hospitals in South Africa (Brink, Messina, Feldman, Richards, Becker, Goff, Bauer, Nathwani & van den Bergh 2016: 1017). The study of Howard, Pulcini, Hara, West, Gould, Harbarth and Nathwani (2015: 1247) identified the common top three barriers to delivering a functional and effective AMS programme in hospitals across all continents except Africa as; a lack of funding or personnel and a lack of information technology or ability to get data, followed by prescriber opposition or other higher priorities. Whilst in Africa information technology is shown to be the main barrier to delivering optimal AMP in hospitals (Howard et al. 2015: 1247).

In addition to the lack of training programs for infectious disease (ID) pharmacists, a low number of ID physicians and the infantile introduction of clinical pharmacy practice are barriers for implementation of AMS in South Africa (Messina, van den Bergh & Goff 2015: 10, 11). Allerberger, Gareis, Jindrak & Struelens (2009: 1181) pointed out that a lack of experts should not be viewed as an insurmountable barrier to implementation of an ASP since such deficit can be overcome by introducing training courses. A study conducted in 47 Netcare private hospitals in seven of the nine South African provinces demonstrated the effectiveness of the antimicrobial stewardship led by non-specialised pharmacists (Brink et al. 2016: 1017). This study showed a significant reduction in overall antibiotic consumption of 18.1% in 116 662 patients in an infectious diseases resource-limited setting (Brink et al. 2016: 1023).

Internationally pharmacists are accepted as equal antimicrobial stewardship partners in ensuring optimal use of antimicrobials (Schellack, Pretorius & Messina 2016: 973). While, in South Africa pharmacists usually provide advice on the rational use and dosing of antimicrobial agents, and write antimicrobial guidelines (Kolman et al. 2016: 26). A recent prospective multicenter study conducted in 33 South African hospitals led by a non-infectious disease pharmacists, showed that non-infectious disease pharmacists can significantly improve the timely administration of antimicrobials to improve patient care and contribute to interdisciplinary engagement between doctors and nurses to strengthen the importance of early administration of antimicrobials to improve patient care (Messina, et al. 2015:12). This study found a significantly improved ‘‘hangtime of antibiotics’ compliance from 41.2% to 78.4% (Messina et al. 2015: 9).

2.12 SUCCESSES OF ASP

The effectiveness of ASP in reducing inappropriate antimicrobial use and the development and spread of antibiotic resistance has been evaluated in numerous published scientific papers. A Cochran review of 89 studies conducted in 19 countries on five continent with the aim of identifying effective interventions in improving antimicrobial prescribing practices, showed that these interventions can reduce antimicrobial resistance or healthcare-associated infections (HAIs) and improve clinical outcomes (Davey et al. 2013: 21) Additionally, the results showed that restrictive interventions work faster than persuasive intervention and that complex, multifaceted interventions were not necessarily more effective than simpler interventions (Davey et al. 2013: 25).

In a qualitative systematic review of 24 studies from 9 different countries including United States, Brazil, Austria, China, France, Tunisia, Hungary, Greece and Germany, a statistically significant reduction in the use of targeted antibiotics was observed in all studies of restriction and pre-approval policies. However, the approach of restricting the use of certain antibiotic classes is associated with a compensatory increase in unrestricted antibiotics (Kaki, Elligsen, Walker, Simor, Palmay & Daneman 2011: 1225, 1229). The study of Kaki et al. (2011: 1225) revealed that computer-assisted decision support, formal reassessment and the impact of an infectious diseases consultant caused a decrease in antibiotic use among several classes of antibiotics. In regard to averting the increase in antibiotic utilization and resistance among unrestricted alternative agents due to the passive restriction policies, the authors recommended more active and interactive stewardship interventions (Kaki et al. 2011: 1229).

A quasi-experimental study of Guerri-Fernandez, Villar-García, Herrera-Fernández, Trenchs-Rodríguez, Fernandez-Morato, Moro, Sancho, Grande, Clara, Grau and Horcajada 2016: 119) demonstrated conflicting results. The study showed a 38% increase in audits with, and a 62% in audits without recommendations to change the prescribed antimicrobial regimen, also an inappropriate prescribing in 26.9% of treatments in the post-intervention period and 37.5% in the intervention were also observed (Guerri-Fernandez, et al. 2016:121). The most frequent reasons for inappropriate treatment were: the deviation from the hospital's antibiotic guidelines,

the wrong dosage as well as lack of antimicrobial coverage. A total of 12 patients died during the study period (Guerri-Fernandez, et al. 2016:121).

Various interventions are multifaceted and while this may increase their effectiveness, the complexity makes it challenging to identify the successful components of the intervention. For example, Filice, Drekonja, Greer, Butler, Wagner, MacDonald, Carlyle, Rutks and Wilt (2013: 1209) in a systematic literature review focusing on the different components of ASP found improvements in antimicrobial prescribing patterns and reductions in antimicrobial resistance as well as costs due to ASPs. This study highlights the equivalent importance of all types of ASP programmes and they are successful in improving antimicrobial prescribing patterns.

Whereas, Boyles, Whitelaw, Bamford, Moodley, Bonorchis, Morris, Rawoot, Naicker, LusakiewiczI, Black, Stead, Lesosky, Raubenheimer, Dlamini and Mendelson (2013:4) found that the use of a 2-part intervention complicated inference about the specific effects of both the chart and the ward rounds (Boyles et al. 2013:7). Although most interventions individually show potential in reducing inappropriate prescribing, this study underscores the complexities brought by a multi-component ASP.

2.13 THEORETICAL FRAMEWORK

Before discussing the methods used in this study the concepts theory and the framework needs to be clarified first to put the adopted framework into context. The theory consists of concepts and a set of propositions that explain or predict events or situations by illustrating the relationships between variables, as well as help to make research findings meaningful and interpretable (Polit & Beck 2010: 195-196). A framework is referred to as a collection of interrelated concepts that underpins a study (Polit and Beck 2010: 198) Therefore, theoretical framework serves as the structure and support for the rationale of the study as well as provide guidance on which to built and support a study (Grant & Osanloo 2014: 12 -13).

This study is guided by the RE-AIM framework for evaluating the impact of health promotion program. This framework offers a comprehensive approach to considering reach, efficacy, adoption, implementation, and maintenance domains, which offer a comprehensive approach to evaluating the impact of an intervention (Glasgow, Klesges, Dzewaltowski, Estabrooks & Vogt 2006:688). Each component of RE-AIM framework addresses a major research question that can guide program planning and evaluation (Ory, Altpeter, Belza, Helduser, Zhang & Smith 2015: 1). Five dimensions of RE-AIM framework to consider for program evaluation are shown in fig. 2.1.

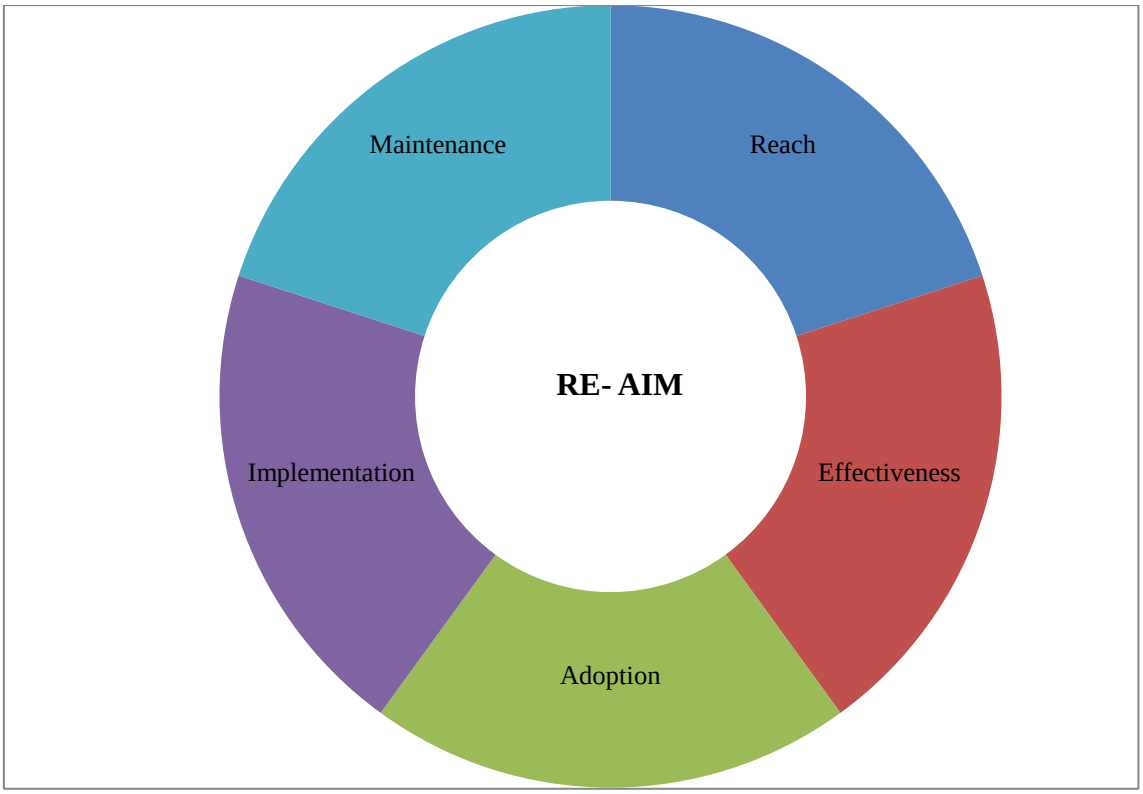


FIGURE 2.1 RE-AIM FRAMEWORK KEY COMPONENTS (Ory, Altpeter, Belza, Helduster, Zhang & Smith 2015:2)**.**

Reach, captures the percentage of people from a given population who participate in a program and describes their characteristics. Knowledge of the number of eligible participants taking part in the program as well as the number of drop-outs or attrition in the program, is important to help measure the success of recruitment, and retention of participants (Ory et al. 2015:2; Sweet, Ginis, Estabrooks & Latimer-Cheung 2014: 74).

Effectiveness refers to the positive and negative outcomes of the program and provides the evidence of the success of the implemented program: whether it performs as expected, which ultimately revealing the program's value and return on investment (Ory et al. 2015:2).

Adoption, is similar to Reach, (Glasgow, Vogt & Boles 1999: 1323) but is assessed at the level of the settings measuring organizational capacity and partnership support including factors such as cost, level of resources and expertise required, size of the adopting organization. It is important to know whether the program is sustainable and the facility has personnel and fiscal support to manage the program, and is located in areas where the target audience resides as well as whether there is the capacity to bring the program to scale (Ory et al. 2015:2).

Implementation, is an indicator of the extent to which different components of an intervention are delivered as intended and its cost (Glasgow, McKay, Piette, & Reynolds, 2001: 120), it is important in identifying areas of need for improvement in program delivery, assuring participant results can be attributed to the program and identify return on investment for stakeholders (Ory et al. 2015:2).

Maintenance operates at both the individual and the system level. At the individual level, maintenance refers to how well behaviour change efforts hold up in the long term. At the organization level, it refers to the extent to which a treatment or practice becomes institutionalized as a routine part of usual care within an organization (Glasgow et al. 2001: 120; Sweet et al. 2014:74-78).

2.14 THE RE-AIM FRAMEWORK FOR IMPACT EVALUATION

Impact evaluation is defined as a systematic and empirical investigation of the impacts produced by an intervention (IE Working group 2012: 2). It assesses the changes in the well-being of individuals that can be attributed to a particular program or policy (Gertler et al. 2016: 4). In addition, AIPC (2003: 5) has suggested the inclusion of the process evaluation, which assesses the information on the process of delivering the program. This is important for measuring the activities and quality of the program or service and who it reaches (AIPC 2003: 5). This was further corroborated in the IDSA/SHEA guidelines that the implementation of an AMP should

include both process and outcome measures to measure the success and the impact on the antimicrobial use and resistance patterns (Dellit et al. 2007: 161).

Gertler et al. (2016:4) point out that well-designed and well-implemented impact evaluation provides comprehensive evidence that can be used to inform policy decisions, shape public opinion, and improve program operations. The authors further state that impact evaluation results are particularly useful when the conclusions can be applied to a broader population of interest (Gertler et al. 2016: 11). The RE-AIM framework adopted for this study is useful for assessing the implementation and performance of interventions in the real-world settings as well as their subsequent impacts at individual and organizational levels (NCCMT 2010:1).

This framework covers the concepts which form the main basis of the entire research (fig 2.1), including: Reach (proportion of the target population that participated), Efficiency of the program (success rate), Adoption (proportion of target settings involved), Implementation (extent to which the program was delivered as intended), and Maintenance (extent to which the program was sustained over time) (Glasgow et al. 1999: 1322). The application of RE-AIM framework has contributed to research on nutrition (Huye, Connell, Crook, Yadrick & Zoellner 2014: 34), diabetes (Compernolle, De Cocker, Lakerveld, Mackenbach, Nijpels, Oppert, Rutter, Teixeira, Cardon & De Bourdeaudhuij 2014: 147), sexually transmitted infection (Jeong, Jo, Oh & Oh 2015:847) physical activity and nutrition curriculum (Dunton, Lagloire & Robertson 2009:229).

2.15 CONCLUSION

Over seven decades of successful antibiotic therapy, microbes have developed strategies to defend themselves from antimicrobials. The burden of resistance is persistently increasing. This afflict is further aggravated by risks factors including immuno-suppression, patients' frail condition, invasive medical devices, overuse, and misuse of antimicrobials in the ICU. Based upon the foundation of the emergence and spread of antimicrobial resistance established in this study, it is clear that unless an effective strategy is devised the scourge will continue to grow to enormous levels. Together, with the understanding of the factors promoting antimicrobial resistance

and having knowledge about the mechanism of bacterial resistance, antimicrobial interventions can help alleviate this scourge.

A well-established programme of antimicrobial stewardship demonstrating positive results is evident around the world. Yet countries in the African continent still lack behind showing a steady growth in the implementation of the ASP. In particular, there is a lack of implementation and impact evaluation studies of the ASM programmes. The recommendations of the guidelines for the appropriate prescribing of antimicrobial (Delitt et al. 2007:159; NDoH 2017: 8), should lead to a well-structured and implemented programme with a strong underpinning for the eradication of antimicrobial resistance.

However, despite all the best intention and efforts on the part of the healthcare professionals, the expected outcomes might not be achievable if the program is not regularly appraised. This shortfall may also have serious and detrimental effects from the perspective of disease management. Therefore, it is important to note that program evaluation is critical in determining the extent to which a program has achieved its intended outcomes and the processes undertaken to achieve these outcomes. Moreover, the availability of resources and the timing of decisions about the programme or policy under investigation must be taken into consideration (Rogers 2014: 2).

CHAPTER 3

RESEARCH DESIGN AND METHODS

3.1 INTRODUCTION

In the subsequent chapter, the impact of ASP and its limitations were discussed and the need for constant evaluation of the programme was highlighted. Therefore, this chapter provides the specific methodological details of the research conducted. It details the approach used and conditions under which the various stages of investigations were carried out, acquisition of the permission to do research, and design of research instrument used to collect the primary data. It further indicates how issues of validity and reliability were addressed. Prior to conducting the study, an ethics clearance was obtained as shown in Annexure A.

3.2 RESEARCH DESIGN

According to Polit & Beck (2010: 222) research design of a study provides the basic strategies that researchers adopt to answer research questions and test their hypotheses. It constitutes the blueprint for the collection, measurement, and analysis of data (Kothari 2004: 31). Furthermore, it provides an outline for conducting a study with effective management of threats to internal and external validity of the study (Burns & Grove 2003:195). In particular, Kothari (2004:33) pointed out that the best research design is the one which minimises bias and maximises the reliability of the data collected and analysed.

3.2.1 Research design and strategy

The purpose of this study was to assess whether the ASP is effective in limiting the spread of antimicrobial resistance. Therefore, a quasi-experimental descriptive quantitative study was undertaken. By definition, quasi-experiments lack random assignment to conditions by which treatment is assigned: control or experiment (Shadish, Cook & Campbell, 2002: 14). These designs aim to evaluate the impact of interventions and are frequently used when it is not logistically feasible or ethical to

conduct a randomized controlled trial of causal research design (Harris, Bradham, Baumgarten, Zuckerman, Fink & Perencevich, 2004:1586-1587). Quantitative method is a systematical process of gathering empirical evidence for a study using a formal instrument and analysed with a statistical procedure (Polit & Beck 2010: 17-18). The researcher and research object are considered independent of each other, and the preferred methodological choice is one of experimentation and testing of a hypothesis (Guba & Lincoln 1994: 109). Furthermore, it has the capacity to generalize findings to individuals other than those who participated in the study (Polit & Beck 2010: 17).

Seeing as quantitative research attempts to establish statistically significant relationships, this approach was followed in this study to answer the research questions restated below (Dawson 2002:15).

1. Do hospitals have the capacity to appropriately prescribe antimicrobials?
2. How appropriate are the antimicrobial prescribing procedures to patients suspected to have hospital-acquired infection 48-72h after admission?
3. What is the incidence of different disease-causing bacteria and antimicrobial susceptibility patterns in patients in the intensive care unit (ICU)?
4. How effective are current antimicrobial stewardship programmes in improving the quality of antimicrobial prescribing in the ICU?
5. What strategies can be implemented to improve the effectiveness of antimicrobial stewardship programmes in reducing the spread of antimicrobial bacteria in patients admitted in the ICU?

Furthermore, an analytical observational technique was utilised in this study to draw inferences from the data regarding existing relationship (Schoenbach 1999: 209). A prospective cohort approach characterised by the identification of study subjects at the starting point of the study and the assessment of their exposure to a risk factor was adopted (Euse, Zoccali, Jager & Dekker 2009: 214). Prospective studies can easily demonstrate that the exposure preceded the disease, thereby strongly suggesting causation (Theise 2014: 200).Furthermore, this approach involves broader inclusion criteria and fewer exclusion criteria, making the results more generalizable to clinical practice (Euse et al. 2009: 216-217). Conversely, the lack of

random assignment in this approach is daunting and makes it impossible to establish causal effects. Therefore, the outcomes observed may be attributable to other variables (confounders) and not to the intervention (Dimitrov & Rumrill, 2003: 160; Euse et al., 2009: 216: Harris, Bradham, Baumgarten, Zuckerman, Fink & Perencevich 2004:1588).

A quasi-experimental study using a single group before-and-after intervention design was undertaken to measure the change resulting from the promotional intervention of appropriate antimicrobial prescribing in critically ill patients. By using quasi-experiment, a causal relationship between an intervention and an outcome can be determined (Harris et al. 2004:1587). These designs are practical as they can be performed in real-life settings and can introduce some research control when full experimental rigor is not possible (Polit & Beck 2004: 186-187).

3.3 RESEARCH METHODS

3.3.1 Study setting

A permission to conduct research was applied for at the healthcare institution using a letter shown in Annexure B. Both the Medical Advisory Committee (Annexure C) and the head of ICU (Annexure D) of Chris Hani Baragwanath Academic Hospital gave permission to conduct this study in the facility. The study was conducted in the adult intensive care unit of an academic hospital situated in Gauteng province, South Africa. This academic hospital provides highly specialised healthcare services, the site for research and serves as the specialist referral centre for regional hospitals and neighbouring provinces (GDoH 2016: 64).

3.3.2 Study population

Population refers to a group of individuals with the same characteristics to which the results of the study may be generalizable (Polit & Hungler 1999: 232). As such, the population for this study comprised all critically ill patients, ≥18 years, admitted to the ICU and prescribed antimicrobials at a public hospital in South Africa. For sampling purposes, this study framed all critically ill patients, 18 years and older, admitted to

the adult ICUs and prescribed antimicrobials at the Chris Hani Baragwanath Academic Hospital situated in Gauteng Province (South Africa).

3.3.3 Sample and sampling

According to WHO (2001: 71) sampling is a process of choosing a representative section of the population for observation and study to produce accurate generalizations about the larger group. Sampling involves two fundamental approaches that include non-probability sampling and probability sampling (Kothari 2004: 58). Under non-probability sampling, the researchers purposively select a sample on the basis that it will be representative of the whole total population (Kothari 2004: 59). Whereas, in probability sampling, each unit in a population has a specifiable chance of being selected and it enables researchers to make accurate assumptions or generalizations from the sample to the population under investigation. Moreover, with this technique, the errors of estimation or the significance of results obtained from a random sample can be measured (Kothari 2004: 60).

A systematic random sample was drawn from a list of all tertiary and academic hospitals in Gauteng Province. Systematic sampling is a technique in which each unit in a population has a specifiable chance of being selected. This technique entails random selection of the first unit and then choosing the remaining units of the sample at fixed intervals. Furthermore, the systematic sample is spread more evenly over the entire population (Kothari, 2004:62). Hospitals were arranged in alphabetical order followed by a random selection of the initial study site. Consequently, two study sites were selected for this study. In addition to having an advantage of reducing sampling bias, this technique ensures that all members of the population have equal chances of being selected.

3.3.4 Sample size and sample size calculation

Sampling is the process of selecting a portion of the population to represent the entire population, such that the researcher can study the smaller group and produce accurate generalizations about the larger group (Kothari 2010: 307). For this study, two academic hospitals situated in Gauteng province, South Africa, which provides

services to a diverse population group, were targeted. The initial study site has approximately 3200 beds, with inpatient utilization rate of 77.7% and an average length of stay of 7.9 days (GDoH 2016: 64). The second study site was a tertiary healthcare facility with about 832 beds and approximately 53 beds in the ICU. This hospital has the inpatient bed utilisation rate of 78.9% and the average length of stay of 8.4 days (GDoH 2016: 62).

Only a single targeted public hospital agreed to participate in this study. The optimum sample size is essential in any research to avoid having a confined sample that may result in under-powering the study and lead to failure to detect the difference in outcomes or having a large sample size that may result in wasted time and money (Pourhoseingholi, Vahedi & Rahimzadeh 2013:14). Accordingly, an adequate sample size to estimate the impact of the program with a good precision was determined. The researcher also attempted to reduce the selection bias and sampling error to ensure a large enough sample size by including all eligible patients admitted to the ICU.

The following formula was used to estimate the sample size

$$N = \frac{(r+1)\,(Z_{\alpha/2} + Z_{1-\beta})^2\,\sigma^2}{r\,(\mu_1 - \mu_2)^2}$$

Assumptions

$Z_{\alpha/2}$ =1, 96 for two-tailed test 0.5

$Z_{1-\beta}$ = 0.84 for power 0.8

$r = n^0 / n^1$: ratio for sample size required for 2 groups, for a single group r=1

σ : pooled standard deviation of 2 groups

$\mu_1 - \mu_2$: difference of means of 2 groups

$ES = \mu_1 - \mu_2 / \sigma$: Effective size = 0.53 based on the data in the published study of Davey et al. (2013: 4).

Assuming common variance of the two groups

Since this is a single group pre-post study the number of participants was calculated as follows (Suresh & Chandrashekara 2012: 9):

$N = 2(Z_{\alpha/2} + Z_{1-\beta})^2 / ES^2$

$N = 2(Z_{\alpha/2} + Z_{1-\beta})^2 / ES^2$

$N = 2(1.96 + 0.84)^2 / (0.53)^2$

$N = 15.7 / 0.280$

N = 56 patients

For the allowance of attrition and withdrawal of participants from the study the sample size was adjusted using the following formula:

$N^1 = N / 1 – q$, where q is the proportion of attrition

Therefore, the sample size thus required was 56/ (1 - 0.1) =62 patience for 10% allowance of the withdrawn subjects and patients lost to follow-up (Habib, Johargy, Mahmood & Humma 2014: 26).

3.3.5 Sample inclusion and exclusion criteria

The medical charts of critically ill patients 18 years and above admitted or transferred to the ICU from other departments in the hospital or other healthcare institutions for more than 48 h, and prescribed antimicrobials within the period of admission were reviewed as part of the study. Patients of both gender and any race were included. Patients were excluded if they did not require admission to the ICU and if they were not prescribed antimicrobials during their stay in the ICU.

The infection control specialist in the ICU was included in the study as an antimicrobial stewardship leader to provide information on the capacity of the facility to prescribe quality antimicrobials.

3.3.6 Data collection method and technique

Accurate data collection is essential to maintaining the integrity of research. This can be achieved through the four core principles: the protection of the welfare and rights of research participants, and to reflect the basic ethical values of beneficence and maleficence, justice and respect for persons (NDoH, 2015:3; Owonikoko 2013: 242).

The welfare and rights of human subjects participating in a study can be protected by being informed about the nature of the research study, including any potential risk and benefits, also by signing a consent form before participating in the study (Bulmer 2008: 63). Beneficence and maleficence demand that participants should not be harmed through the conduct of the study (Owonikoko 2013: 242). To accomplish this principle, research must be designed to minimize risk and participants must be made aware of the potential benefits and risks (ACFID 2017:4). While justice principle demands a fair distribution of and access to the benefits of participation in the research (ACFID 2017: 5; NDoH 2015: 5).

3.3.6.1 Data collection instrument

This study set out to collect information about the performance of implemented ASP in an academic hospital. The patients' data were collected through the review of medical records using paper-based questionnaire. The questionnaire was developed based on the reviewed literature, existing surveys and published guides pertaining to the ASP (CDC 2014: 12; Dellit et al. 2007:159; PHE 2015: 12-17). The developed questionnaire consisted of three phases with a total of 57 items. The first phase included 19 items designed to collect information concerning the appropriateness of antimicrobials prescribed in the ICU and patients' demographic characteristics. The second phase included 12 items concerning the outcome of the patients treated with antimicrobials. The third phase included 26 items about the capacity of the hospital to appropriately prescribe antimicrobials.

Given that questionnaires can collect large amounts of information from a large number of people in an efficient and economical way, this method best suited the present study (Mathers, Fox & Hunn 2007: 6). Albeit, closed-ended questions limit the respondents to the options provided, the majority of the questions in the questionnaire were closed-ended questions with either 'yes or no' answer and choosing one alternative from three to more options (multiple choice) (Siniscalco & Auriat 2005: 24). Additionally, certain questions were provided with the option "please specify" so as not to limit participant's responses to pre-defined answers.

Using a standardized questionnaire makes the collected data comparable to the data set and reduces the chance of evaluator bias (Bird 2009: 1308). As the study was

carried out in the natural setting, administering the questionnaire did not interfere with the daily routines of the settings (Mathers, Fox & Hunn 2007: 6).

In addition, as this study gathered sensitive patients' information; using questionnaires helped in maintaining such information anonymous and confidential (CDC 2008: 1). The use of close-ended questions restricts respondents to a fixed, manageable set of responses, which allows the inclusion of more variables. As such, the weakness of closed-ended questions is in providing insufficient information on context. Furthermore, due to the imprecise and unambiguous wording on the questionnaire, participants inaccurately interpret the questions thus establishing bias in responses (Siniscalco & Auriat 2005: 23- 24)

3.3.6.2 Content validity of the instrument

The questionnaire was not entirely a new creation, it was developed using the components of AMS that had been identified in ASP guides and from questions asked in published questionnaires and toolkits (see section 3.2.4.1). As noted by Chiwaridzo, Chikasha, Naidoo, Dambi, Tadyanemhandu, Munambah and Chizanga (2017: 4) literature does not specify the number of content expects needed to validate a study, as such 5 ICU nurses were requested to participate in content validation of the tool.

The initial questionnaire was distributed in July 2017 to 5 ICU nurses (experts) to test for the readability and clarity of the questions. Following the COnsensus–based Standards for the selection of health status Measurement INstrument (COSMIN) checklist with some modifications as depicted in Table. 3.1 (Mokkink, Terwee, Patrick, Alonso, Stratford, Knol, Bouter, & de Wet 2012: 30), the face and content validity of ASPAQ tool was assessed. The discussions with the experts highlighted three main issues which required attention before the commencement of the main study.

TABLE 3.1 FACE AND CONTENT VALIDITY CHECKLIST

General requirements	Yes	No
1. Are the words simple, direct and familiar?		
2. Are the questions clear and simple?		
3. Are there any questions with a double meaning?		
4. Are there any biased questions?		
5. Are there any leading questions?		
6. Are the questions sensible to all respondents?		
7. Can the questions be shortened without losing meaning?		
8. Are all questions relevant for measuring the impact of ASP on reducing the incidence of hospital-acquired antimicrobials?		
9. Are all the questions in phase 1 and phase 2 relevant for the study population, critically ill patients in the ICU?		
10. Are there any questions you wish to add to the questionnaire?		

The length of the questionnaire was the first issue identified, and the panel suggested that it needed to be shortened to encourage quick completion of the questionnaire thus reducing weariness of the data collector. The other concern was the repetition of questions which made the questions redundant and adding to the length of the questionnaire. Such questions were removed from the questionnaire.

Among the checklist's items the experts established, the experts could not reach a consensus on item 7 (table 3.1). The researchers decided not to shorten the questions.

The participating nurses were given an information cover letter (Annexure E), consent form (Annexure F) the copy of the questionnaire and the checklist (Table 3.1). The cover letter included the purpose and objective of the study, the reasons for selecting the nurses, the outline of the questionnaire and the content evaluation procedure. Each nurse was asked to read the questionnaires and fill the checklist as

well as comment on the relevance, ambiguity, and ease of comprehension of the items. The nurses were chosen because of their knowledge in the daily running of the ICU, and the use of antibiotics in the ICU. Responses to the questionnaire were considered and amendments were made. The questionnaires were revised until no further amendments could be made to the questionnaire.

The final and adapted questionnaire was 8 pages long with 41 items (Annexure G). Phase 1 had 11 items, phase had 7 items and phase 3 contained 23 items. The researcher was trained by ICU nurses on reviewing patients' charts and extracting relevant information. For the ease of collecting data and not interfering with the daily running of the unit the data was collected during the visiting time and when doctors have completed their morning rounds. Data was collected on weekdays. Information on the capacity to prescribe appropriate antimicrobials was obtained from the head of the ICU department. An invitation letter, consent form and phase 3 of the questionnaire were given to the member of ASP team of the ICU for completion.

3.3.6.3 Problems experienced during data collection

No apparent problems were encountered during data collection, except that some patients had reservations for participating in the study because of fear of divulging their medical information to a stranger. When the consent form was explicitly explained to them they gave their consent. Additionally, it was difficult to avoid interfering with doctors' rounds as there was no time set for such rounds. Microbiological results such as the susceptibility test results needed Doctors' code to be accessed, making data collection difficult.

3.3.7 Methods of data analysis

The data from the questionnaire were statistically analyzed primarily focusing on the study questions specified in chapter 1.

Research question 1: Do hospital have capacity to appropriately prescribe antimicrobials?

In regard to assessing the capacity to prescribe prudent antimicrobials the core elements of hospital antibiotic stewardship program identified by the (CDC 2014: 4)

were used. The core elements of hospital antibiotic stewardship programs, include, Leadership commitment; accountability; drug expertise; action; tracking; reporting and education (CDC 2014: 4). Therefore, for the purpose of this study, the capacity of the hospital to prescribe appropriate antimicrobials will be determined by assessing seven core elements of hospital antibiotic stewardship programs with a series of criteria as depicted in (Annexure I). Each core element was measured by calculating the score of the criteria of the above-mentioned core elements. Each criterion within a core element was scored as either Yes or No. To provide a comprehensive assessment, total scores of each category were added together and converted into percentages. The capacity of each core element can be characterised as deficient (0 – 25%), Low (26 – 50%), sufficient (51 – 75%) or satisfactory (76 – 100%).

For study questions 2 and 3 a data dictionary was created to organize data entry, as part of a validation plan and for statistical analysis (Elliott, Hynan, Reisch & Smith 2006: 335). Patients' primary diagnoses were grouped into major diagnostic categories (WHO 2016: 99-791). Five categories were appropriate for use in this study, these included the disease and disorder of the 1) respiratory system, 2) digestive system 3) circulatory system 4) Genitourinary system and 5) Injury, poisoning and other sequences of external causes. The data dictionary provided detailed information about the data, such as definitions of all data attributes, their meanings, and values (Annexure H).

Research question 2: How appropriate are the antimicrobial prescribing procedures to patients suspected to have hospital-acquired infection 48- 72 h after admission?

The method developed by Gyssens, Van den Broek, Kullberg, Hekster and Van der Meer (1992: 724) as cited by Baktygul, Marat, Ashirali, Harun-or-Rashid & Sakamoto (2011: 159) was followed to assess the appropriateness of antimicrobial prescriptions in the ICU. For appropriateness of the prescription the following parameters were assessed: correct dosage, interval, routes of administration and appropriate length of treatment.

Following the classification of prescriptions given by Baktygul et al. (2011: 159), prescriptions were considered therapeutic if (a) the medical record contained information that the antibiotic was prescribed for therapy, or (b) an infectious disease was diagnosed, or (c) clinical signs of an infection were present on the day that antibiotic therapy was initiated.

Furthermore, the use of prophylactics were explained to elucidate the difference from antibiotic therapy and prophylaxis following the method of Baktygul et al. (2011: 159), wherein prophylactic is indicated if (a) the medical record stated that the antibiotic was prescribed for prophylaxis or (b) it was given for only one day relative to the timing of a surgical intervention (Baktygul et al. 2011: 159). The prescription of antimicrobials was judged according to local antimicrobial guidelines.

Research question 3: What is the incidence of different disease-causing bacteria and antimicrobial susceptibility patterns in patients in the intensive care unit (ICU)?

The incidence of different bacteria and their susceptibility to antimicrobials were assessed by determining the distribution of the bacterial isolate from microbiological samples amongst patients, the frequency of different bacteria isolated from patients admitted in the ICU, and the microorganisms' susceptibility against antimicrobial treatment.

All patients with positive microbiological cultures were considered for this section of the study. Infection rates per 100 patients were calculated by dividing the total number of patients with HAI by the number of participants (X100). The association between the HAI and potential risk factors was assessed using Chi-square test in univariate analysis (Shao, Ni, Goa, Wei, Zong, Meng, Yang & Liu 2016: 23644).

The hypothesis regarding the association between potential risk factors and the development of HAI was tested:
H_0: There is no association between the potential risk factor and the incidence of HAI.
H_1: There is an association between the potential risk factor and the incidence of HAI.

If the calculated Chi-Square value is smaller than the critical Chi-square value (X^2 < 0.05) then the null hypothesis is not rejected.
If the calculated Chi-Square value is equal or larger than the critical value (X^2 ≥ 0.05) then the null hypothesis is rejected.
If p ≤ 0.05, the association is statistically significant
If p > 0.05, the association is not statistically significant

Research question 4: How effective are current antimicrobial stewardship programmes in improving the quality of antimicrobial prescribing in the ICU?

The RE-AIM framework has been developed to enhance the impact of health promotion programs by focusing on 5 dimensions including reach, efficacy, adoption, implementation and maintenance of these programs (Brunisholz, Kim Savitz, Hashibe, Gren, Hamilton, Huynh & Joy 2017: 2; Glasgow et al., 1999: 1322; Lee, Golaviz, Soltero, Chavez, Jauregue, Hernandez, Taylor & Estabrooks 2017:2). It provides a model to inform the design, implementation and evaluation of a health program (Lee et al, 2017: 2). Additionally, it can be used for evaluating the reach, impact and implementation of the program at individual level focusing on reach and effectiveness; organizational level focusing on adoption and implementation, and at both individual and organizational levels involving maintenance of the program (Jauregui, Pacheco,Soltero, O'Connor, Castro, Estabrooks, McNeil & Lee 2015: 163).

For this study, both individual and organization levels of the program were evaluated. This was achieved by using all 5 dimensions of the RE-AIM framework to assess the impact of the ASP in improving the quality of antimicrobial prescribing in the ICU. A detailed description of the RE-AIM dimensions and application in this study is given in (Table 3.2). The impact of ASP was calculated by adding the scores on the five RE-AIM dimensions and dividing them by 5 (Compemolle, De Cocker, Lakerfeld, Mackenbach, Nijpels, Oppert, Rutter, Teixeira, Cardon, & De Bourdeaudhuij 2014:151).

TABLE 3.2 OPERATIONALIZATION OF THE 5 RE-AIM DIMENSIONS FOR THE IMPACT OF ASP.

RE-AIM DIMENSION	DEFINITION	GUIDING QUESTIONS	EVALUATION CRITERION	INDICATORS
REACH	Percent and characteristics of participating critically ill patients admitted to the ICU.	Who amongst the critically ill adults ≥ 18y admitted in the ICU of Gauteng public hospitals benefited from the program?	The total number of eligible participants minus the number of declined patients. Demographic information.	Gender. Level of education. Ethnicity. Marital status. Diagnosis. Percent of participants.
EFFECTIVENESS	A measure of health effects of antimicrobials prescribed for critically ill adults in the ICU.	What proportion of critically ill adult patients developed adverse events or acquired antimicrobial-resistant infection?	A measure of primary outcome. Positive outcomes minus negative outcome.	Mortality Quality of care. Safety of care. Risk factors
ADOPTION	An organizational measure of the eligible hospitals and program delivery agents (ASP team members)	How many hospitals are participating and how equipped are these settings?	The proportion of participating settings including their capacity to prescribe quality antimicrobials.	In-house microbiological laboratory. Human resources. Level of expertise of the team members. List of essential antimicrobials. Evidence –based local antimicrobial guidelines.
IMPLEMENTATION	An organizational measure of the extent to which the AS program is delivered as intended.	What proportion of the procedures of prescribing antimicrobials in the ICU are followed?	The number of activities completed for appropriate prescribing of antimicrobials.	Microbiological tests. Antimicrobials indicators. Appropriateness of therapy. Review of therapy.Duration of therapy.

Reach was calculated by counting the number of willing and participating patients and dividing this value by the total number of eligible recruited patients. Effectiveness was calculated by counting the number of patients who developed HAI, subtracting that number from the total and divided this value by the total number of participating patients.

The number of patients belonging to the race that were risk factors for the development of HAI was subtracted from the total number of participating patients and the difference divided by the total number of participants. The number of patients prescribed appropriate antimicrobials was divided by the total number of participating patients.

Adoption was calculated as the number of the hospital which accepted the invitation to participate in the study divided by the total number of eligible hospitals recruited. The number of individuals who constituted multidisciplinary ASP team members was divided by the recommended number of ASP team members. Implementation was rated by assessing the steps taken to prescribe appropriate antimicrobials as specified in the guidelines (Wasserman, Boyles & Mendelson 2014: 6 – 10), then dividing that value by the total value of the steps required for prescribing appropriate antimicrobials. The maintenance domain was excluded because the duration for the collection of data was shorter than 6 months, the period required to measure the long-term effects of a program as well as, the program sustainability which is the extent at which the program is still ongoing ≥ 6 months after the study completion.

Research question 5: What strategies can be implemented to improve the effectiveness of antimicrobial stewardship programmes in reducing the spread of antimicrobial bacteria in patients admitted in the ICU?

As per the results obtained in question 1, the characteristic of each capacity area determined the strength and weaknesses of the organizational capacity and provided the information whether the capacity areas warranted any corrective measures. The factors that affected the organizations capacity were highlighted from the scores of the capacity areas to optimise the appropriate use of antimicrobial. Capacity areas with a diminished performance capacity were identified and a strategy was devised that focused specifically on improving the organizational performance on prescribing quality antimicrobial agents. The following components of action plan were utilised (Catholic Relief Services 2011: 12)

- The description of the capacity with a weakness.

- The improvement and capacity strengthening the effort
- Steps necessary to improve the capacity.

3.3.7.1 Cross-checking data for completeness

Data errors can occur during data transfer and management processes leading to data loss, incomplete or inaccurate data (Amoakoh-Coleman, Kayode, Brown-Davies, Agyepong, Grobbee, Klipstein-Grobusch & Ansah 2015:1-2). Such errors can be reduced and verified using logic checks: to determine the status of data that are not logically sound and can be performed by range checks, detection of outliers and checking for relational conflicts; visual data verification which can be carried out by comparing the data from the database with the source data, while the double data entry method compares two databases are compared electronically to facilitate the detection of data entry errors or a combination of them (Fong 2001: 843).

For this study, a double data entry technique was used to check for the data completeness. Data were entered twice and the two data sets were compared, differences were examined, noted and corrections made.

3.3.7.2 Data coding

The responses to most items related to the capacity of the institution to prescribe quality antimicrobials (phase 3 of the questionnaire), were NO / YES and were allocated the score of 1 and 0 respectively to facilitate data analysis and interpretation. For item 1 all responses were allocated a score of 1. Items 2 and 12 with responses Never, Seldom and Frequent were allocated scores 0, 1 and 2 respectively. Item 6 responses, Own funding, and Sponsor were allocated scores of 0 and 1 respectively.

3.3.7.3 Data entry

Data were entered into Microsoft Excel 2007 (Microsoft Corporation, Redmond, WA) and analyzed using SPSS version 24 for Windows (Amonk, NY: IBM Corporation, USA).

3.3.7.4 Analysing data

The data extracted from patients' charts were analyzed to summarize and describe it and to facilitate answers to the research questions through its examination and interpretation.

3.3.7.4.1 Statistical methods used in data analysis

Descriptive data were presented in frequencies and percentages with mean and standard deviation to summarize the data. Continuous variables were expressed as the mean and standard deviation.

Multivariate logistic regression analysis was used to determine the relationship between the patient-specific factors and the occurrence of hospital-acquired infections (HAI). Standard methods were used to calculate 95% confidence intervals (CIs) for the proportion of patients who received antimicrobials in the ICU (Baktygul et al. 2011:160). The following variables were investigated as confounding factors (the variable that distorts the association between the exposure and the outcome) (Kamangar 2012: 308), for hospital-acquired infections: age, gender, and chronic disease, and these confounding factors were compared between patients.

3.3.7.4.2 Presentation of results

The results of the study were graphically presented to identify patterns and trends as well as relationships within the data. Categorical data were displayed using a bar chart, while histograms were used to display the distributional form of continuous data. In addition, the association between two continuous variables was visually examined by constructing scatter-plots.

3.4 MEASURES TO ENSURE VALIDITY AND RELIABILITY

Ensuring the integrity and quality of data collection is part of good data management (Peersman 2014:7). The two crucial aspects of ensuring quality in the evaluation of a measurement instrument are identified as validity and reliability (Tavakol & Dennick, 2011: 53). Furthermore, it is pointed out in the literature that an instrument cannot be valid unless it is reliable (Tavakol & Dennick 2011: 53), but an instrument can be reliable without being valid (Kimberlin & Winterstein 2008: 2278).

3.4.1 Validity

The validity of an instrument has been generally described as the evaluation of the degree to which the instrument measures what it is intended to measure (Alumran, Hou & Hurst 2012: 223; Kimberlin & Winterstein 2008: 2278; Moussaoui, Opmeer, Bossuyt Speelman, de Borgie & Prins 2004: 592). In addition, Cook and Beckman (2006: 8) describe validity as the degree of the trustworthy of the test results as interpreted for a specific purpose. Christensen, Johnson, and Turner, (2015:158) noted that the more evidence of validity is provided, the more trustworthy the interpretations based on the measurement scores will be.

There are several ways to assess the validity of a test including face validity, content validity, construct validity and criterion validity (Bolarinwa 2015: 195). Content validity measures the adequacy with which the test items comprehensively and representatively sample the content areas to be measured (Anyanwu & Williams 2015: 3). Criterion validity assesses whether scores of new instrument agree with an accepted measurement of the same theme. It may be divided into the concurrent validity and predictive validity depending on the condition of the state whether current or future (McDowell 2006: 31). Construct validity has been defined as the extent, to which an operationalization measures the construct it is supposed to measure (Pennings & Smidts 2000: 1338).

For this study factor analysis was performed. This technique can be applied as an exploratory factor analysis (EFA), wherein the number of observed variables is reduced into a smaller number of construct variables by examining the co-variation among the observed variables (Schreiber, Stage, King, Nora & Barlow 2006: 323). In addition the variables that are more important for measuring construct variables were established, thus organising those variables in a way reflecting the latent variable (Williams, Onsman & Brown 2010: 2). It can also be used as a confirmatory factor analysis (CFA) for confirming that the original variables reflect the latent variable as assumed, thus establishing validity evidence based on the internal structure of measuring instrument (Wetzel 2011: 31).

In this study the exploratory factor analysis technique was undertaken to identify the variables that group together (Dhillon, Zaini, Quek, Singh, Kaur & Rusli 2014: 846).

Exploratory factor analysis was considered appropriately as there was no prior knowledge about the number of underlying factors that could be found to explain the data. The data were screened for factorability using several criteria including sample size, participants to variable ratio, correlation matrix, multicollinearity and singularity, anti-image correlations, Kaiser–Myer–Olkin (KMO) measure of sample adequacy and Bartlett's test of sphericity.

First, the correlation matrix was analysed to verify the pattern of inter-correlations between the measured variables to justify factor analysis (Watkins 2018: 226). The Kaiser Meyer Olkin (KMO) and Bartlett's sphericity test of sampling adequacy were used to determine the factorability of the matrix and data as a whole (Zulkepli, Sipani & Jibril 2017: 14). The recommended value of KMO> 5 (Field, 2000: 446), and the Bartlett's sphericity test that should produce a statistically significant chi-square value ($p< 0.05$) to justify the application of EFA (Pinto, RO, Pattussi, M P, do Prado Fontoura, L, PolettoI, S, Grapiglia, V L, Balbinot, A D, Teixeira, V A & Horta, R L. 2016: 3).

In order to determine the number of factors to retain for subsequent investigation, the Eigenvalues criterion >1 and the scree plot were considered (Watkins 2018: 230). The eigenvalue was assessed to determine the contribution of the factor to the model, with values <1 suggesting a low contribution to the model (Pedrosa, Rodrigues, Padilha, Gallani & Alexandre 2016: 652). In addition, the components of interest were rotated based on the eigenvalues over 1 criterion and the scree plot. An Oblimin (Promax) rotation was carried out to enhance interpretability of factor structure and to provide additional information on the correlation between factors (Wetzel 2011: 37).

Subsequently, item communalities were determined to confirm whether all factors extracted from this analysis were reliable to be considered for further analysis (Zulkepli, Sipan & Jibril, 2014: 14). Communality shows how much of the proportions of the variances for each variable are explained by the extracted components (Al-Durgham &. Barghash 2015: 298). Item communalities of > 0.3 was considered an acceptable value (Mansor, Haque, Sheikh, Choon & Zin 2016: 359; Zulkepli, Sipan & Jibril 2014: 14). Higher communality values suggest a larger contribution of the

variance in the variables that has been accounted for by the extracted factors (Mansor, Haque, Sheikh, Choon & Zin 2016: 359).

To ensure that each item corresponded to the construct's underlying structure, a factorial load criteria equal to or greater than 0.4 was considered so that the item belonged to the construct (Pinto, Pattussi, do Prado Fontoura, PolettoI, Grapiglia, Balbinot, Teixeira & Horta 2016: 5).

The validity of the tool is determined by the load value of each item, representing the correlation between the item and the related factor (Cecchetto & Pellanda 2014: 418; Reichenheim, Hokerberg & Maraes 2014:929). Items with the loading value of > 0.3 are regarded as tolerable, whereas values ranging from 0.35 to >0.5 are regarded as fair, values between 0.5 and 7 as moderate and loading of 7 and above are good loadings (Reichenheim et al. 2014: 929 – 930).

However, factor analysis could not be performed with the data collected from the ASP team member because of a very low sample size (single ASP member). Since the questionnaire was constructed to evaluate the impact of ASP on the antimicrobial prescribing, and on the premise that ASP aims to optimise patients' outcome while minimizing unintended consequences of antimicrobial use, Phase 1 and Phase 2 of the questionnaire were used.

3.4.1.1 Internal validity

Internal validity is defined as the degree to which observed changes in outcomes can be correctly inferred to be caused by an exposure or an intervention (Harris, McGregor, Perencevich, Furuno, Zhu, Peterson & Finkelstein 2006:18). It assesses whether the measures obtained from the research were actually quantifying what it was designed to measures (Bolarinwa 2015: 195).

All patients' data were collected by the researcher personally to eliminate most threats, such as the inter-rater effects and testing effect to the internal validity of the scores. There was no unanticipated event that occurred during data collection. A standardized instrument was used to collect patients' data to reduce changes in the instrument measurement.

3.4.1.2 External validity

External validity refers to the degree to which the results can be generalized to and across individuals, settings and times (Carlson & Morrison 2009: 81). Furthermore, internal validity is a prerequisite for external validity (Carlson & Morrison 2009:81).

Although getting subjects to participate in a study that involves chart review can be difficult, the charts of all excluding three of the eligible patients who were approached to participate were reviewed. Three patients refused to take part in the study. To protect from sampling bias this study included critically ill adult patients of ≥ 18 yrs, of both sex, and any race, admitted to the ICU from other wards or transferred from nearby health care institutions, as well as prescribed antimicrobials.

3.4.2 Reliability

Reliability refers to the degree to which measures are free from error and it pertains to the consistency, or reproducibility of test score (Thanasegaran 2009:35). In accordance, the less consistent a given measurement is, the less useful it renders the data to be analyzed.

There are several measures for evaluating the reliability of test scores: the measure of stability which involves the evaluation of the correlation of measures across time or evaluators, for example test-retest and inter-rater reliability; the measure of equivalence which involves the evaluation of a correlation between two sets of instruments such as split-half and parallel forms as well as internal consistency which measures the degree in which scores measure the same concept. It involves correlation among all items (Kimberlin & Winterstein 2008: 2277).

3.4.2.1 Testing the reliability of the data collection instrument.

The reliability of ASPAQ was assessed by means of the internal consistency using a variety of parameters (Thanasegaran 2009: 36); item-total correlation, inter-item correlations and Cronbach's alpha (α). The internal consistency of the items was estimated by using Cronbach's apha coefficient for the entire scale and the extracted factors. For the questionnaire to be considered reliable, the item total correlation should be >0. 50; the inter-item correlation should fall in the range 0.15 – 0.85 and

Cronbach's alpha be > 0.6 (BrckaLorenz, Chiang, Nelson & Laird 2013: 1; Cecchetto & Pellada 2014: 418)

3.5 ETHICAL CONSIDERATIONS

3.5.1 Research ethics

Research in the critical care environment is essential to inform best practice, but it is confronted with ethical challenges, such as the ability of a patient to make a rational informed decision, research related risk of harm, research related exploitation and coercion (Morrow 2015: 34). To ensure the maintenance of ethical integrity of this study the researcher considered several ethical principles as discussed in the following sections.

Considering the autonomy principle (Morrow 2015:34; Norris, Jackson & Khoshnood 2012: 4; Summers 2009:49), the researcher took special measure to ensure that participation in the study was voluntary. The researcher provided eligible participants with adequate information about the risk, benefits, duration, and the purpose of the study and the role of the participants. The eligible participants were informed of their rights to voluntarily participate or decline to participate or withdraw from participation at any time, thus allowing them to voluntarily choose to or not to participate.

Informed consent is important in the research fraternity to inform potential participants, through documents and discussion, of the purpose, procedures, risks, potential benefits, and voluntary nature of the proposed research, and documenting the participant's agreement (WHO 2013:21). In order for a consent to be valid it must include; adequateness, voluntariness, and competence (EC 2010:37). Namely, the prospective participants must: have intact decision-making capacity; be legally competent; be fully informed; be able to communicate a decision; and offer the consent voluntarily, without any implicit or explicit coercion or undue influence (EC 2010:37; Morrow 2015:34). Critically ill or injured patients may not be able to communicate fluently or may have limited understanding of the information provided to them or have sufficient decision-making ability, therefore in such situations a proxy consent; whereby a family member or guardian can sign on behalf of the participant, could be considered (Morrow 2015:34).

Confidentiality was also considered (Norris et al. 2012: 4). Each participant signed a questionnaire which was collected and stored. Different containers were used for both consent forms and the completed questionnaires, to ensure that no signed consent form could be linked to any specific questionnaire. Furthermore, participants' privacy (Norris et al. 2012: 4) was guaranteed by removing names and other identifying information from the data and any report of the study. To preserve the integrity and privacy of data, the collected data were also stored securely in a password protected computer.

Considering beneficence (Norris et al. 2012:4), the results of the study will benefit patients in the future if the guidelines of appropriate antimicrobial prescribing are followed as promoted by the antimicrobial stewardship, subsequently reducing antimicrobial resistance bacteria.

Another consideration of the ethics was the distribution justice (NDoH 2015:5). The study aimed to add to the knowledge on the appropriate antimicrobial prescribing in the ICU and especially of South African hospitals. The ICU patients were selected solely for the reason directly related to the problem being studied: quality of appropriate antimicrobial prescribing, rather than factors like easy availability and vulnerability of the patients. To ensure fair distribution of the benefits of research all races and gender were included to participate in the study.

3.5.2 Participants consideration

The ICU management and shift managers gave the researcher permission to collect patients' data before the commencement of the study. Informed consent was obtained from patients or relatives before commencing with the study. In addition, the Head of the ICU Department and ICU nurses gave informed consent before participating in the study.

3.5.3 Researcher consideration

The researcher collected data by reviewing patients' charts in a way that did not harm anyone. The collected data were not manipulated or altered in any way that might impact or falsely influence the results. There is no conflicting interest that might

interfere with the ability to conduct the study objectively and /or compromise the integrity of the study results.

3.5.4 Institutional consideration

Ethical clearance of the study was obtained from The University of South Research ethics Committee-Department of Health Studies (Annexure A).

Approval for the study was obtained from The Medical Advisory Committee of Chris Hani Baragwanath Academic Hospital in the Gauteng Province (Annexure B).

Site permission to conduct the study was obtained from Chris Hani Baragwanath Academic Hospital Intensive Care Unit (Annexure C).

3.6 CONCLUSION

This chapter has outlined the processes used to collect information for solving the research problem specified in this study. The methodology, study design, sampling techniques and sample size were described. The inclusion criterion used for the selection of the participants, the data collection tools used, method of data collection and analysis, as well as the credibility of the data, were also undertaken.

In the next chapter, the key findings of the study will be reported based on the methodology applied to gather the data.

CHAPTER 4

RESULTS

4.1 INTRODUCTION

This chapter discuss the findings of the data analysis and interpretation with reference to different research questions of the study. The purpose of this study was to evaluate the impact of antimicrobial stewardship program in limiting the spread of antimicrobial resistance in South African hospital, with the aim of identifying its deficiencies so as to act on them and improve their performance. The study site included in the study was selected from 8 academic hospitals in the Gauteng Province. The participating hospital had a total of 18 beds in the general ICU.

Over the study period (1 July – 10 October 2017) a total of 65 patients who had been admitted for at least 48 h and prescribed antibiotics, were identified and recruited. However, 3 (4. 62%) of the 65 identified patients declined to participate in the study. Ultimately, data were collected from 62 (95. 38%) medical charts of patients admitted to the general ICU at Chris Hani Baragwanath Academic Hospital (CHBAH). Of the reviewed 62 charts, 3 (4. 84%) were missing data and deemed unusable. as such were excluded from data analysis

This chapter starts with the statistical description of the data, showing the mean, standard deviation, variations, kurtosis and skewness of the data. Clinical and demographic characteristics of the study population including information on age, gender, race, level of education and admission condition are discussed next then followed by a detailed description of the results relating to the research questions.

4.2 DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

This set of data was intended to describe demographic variables of the sample to assess the representativeness of the participants and the variables' influence on the outcome of the patients.

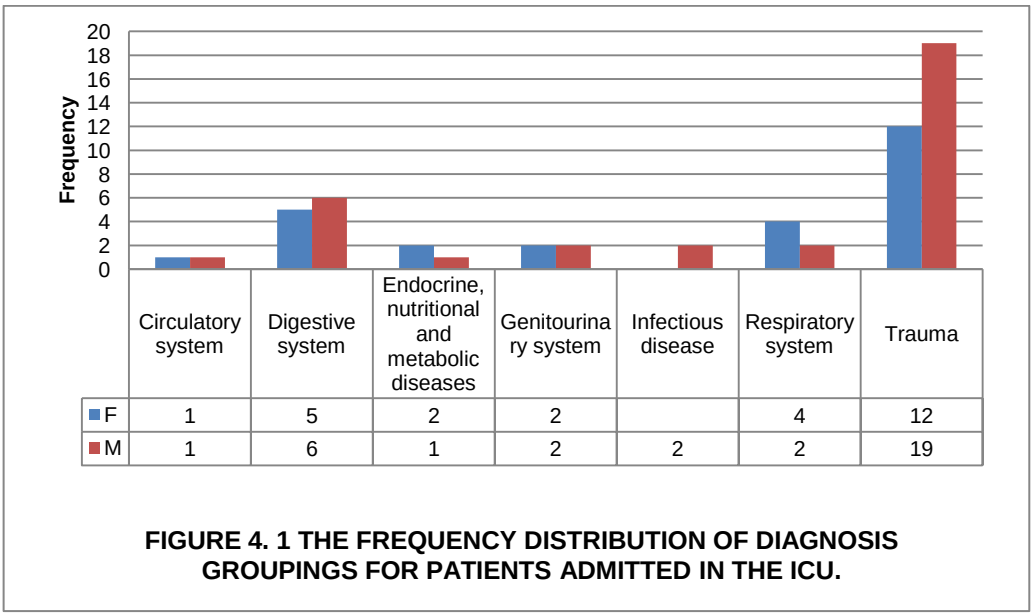
TABLE 4. 1 DEMOGRAPHIC AND CHARACTERISTICS OF THE SURVEYED PATIENTS (n = 59).

Variables	Frequency (%)	
	n	%
GENDER		
Male	33	55.93
Female	26	44.07
AGE (41.51± 16.63)		
19 –38	34	57.63
39 –58	16	27.10
59 – 78	7	11.86
79 –98	2	3.39
RACE		
Black	48	81.36
Coloured	3	5.08
Whites	6	10.17
Indian	2	3.38
EDUCATION		
Primary	0	0.00
High school	32	54.37
FET/ College	20	33.90
University	7	11.86
MARITAL STATUS		
Single	32	54.37
Married	23	38.98
Divorce	2	3.38
Widowed	2	3.38
DIAGNOSIS GROUPING		
Infectious diseases	2	3.39
Genitourinary system	4	6.78
Respiratory system	6	10.16
Digestive and liver	11	18. 64
Trauma	31	52. 54
Circulatory system	2	3. 39
Endocrine, nutritional and metabolic	3	5. 08
SEVERITY OF ILLNESS		
Minor	13	22. 03
Moderate	27	45. 76
Major	18	30. 51
Catastrophic	6	10. 17

The demographic data involved information on age, sex, marital status, and ethnicity as well as the socio-economic status of study population including; educational level,

chronic disease and admission condition. Table 4.1 shows the demographic characteristics of the participants. The final number of patients' charts reviewed comprised of 59 participants with 6 (10.17%) catastrophically ill, 18 (30.51 %) critically ill and 27 (45.76 %) moderately ill patients. The majority of participants were males 33 (55. 93%), and over half of the patients were between 19 – 38 yrs of age. This was a surprising finding since females tend to be sicker than males due to biological differences between males and females. The mean patient age was 41.51 years and they ranged between 19 to 88 years of age.

Of the 59 participants, Indian patients comprised of 2 (3.38 %) participants whereas blacks comprised the majority with 48 (81.36 %) of participants. Six (10.17 %) of the participants were white, followed by 3 (5.08 %) coloured participants. This finding was expected, considering that the hospital is situated in a black populated neighbourhood, albeit patients from other healthcare institutions are transferred to this hospital.



	Circulatory system	Digestive system	Endocrine, nutritional and metabolic diseases	Genitourinary system	Infectious disease	Respiratory system	Trauma
F	1	5	2	2		4	12
M	1	6	1	2	2	2	19

FIGURE 4. 1 THE FREQUENCY DISTRIBUTION OF DIAGNOSIS GROUPINGS FOR PATIENTS ADMITTED IN THE ICU.

Since people who are more educated tend to be more aware of health risks and ordinarily make healthier and positive choices, the highest qualified patients were expected to comprise the fewest of the patients admitted in the ICU. This study showed the majority (n= 32, 54.37%) of the participants admitted in the ICU reached

high school level in education, followed by FET/College educated participant (n= 20, 33.90%). Only 7 (11.86%) patients were highly qualified with university qualifications.

Most participants were diagnosed with trauma (n=31, 52.54%) followed by digestive and liver diseases (n= 11, 18.64 %) and, disease of respiratory system (n= 6, 10.17 %). The majority of male patients 19 (32.20%) were diagnosed with trauma, and 12 (20.33 %) female patients were also diagnosed with trauma as shown in figure 4.1. Fewer patients 2 (3.39 %) were admitted with the diseases of the circulatory system comprising of 1 male and 1 female patients (Figure 4.1).

4.3 STATISTICAL DESCRIPTION OF THE DATA

This section discusses the distribution, central tendency and the dispersion of the data collected from medical records of patients admitted to the ICU. The descriptive statistics for each of the 13 ASPAQ items are presented in table 4.2. Item 6 (severity of diseases) with, a scale of 1- 4, had the highest mean value of 2.32 (Table 4.1).

Subsequent high mean values were observed for clinical indications with a scale of 1-3 and a mean value of 1.377, followed by length of treatment (1.607) in the scale of 1-3, then susceptibility results (1.246) in the scale of 0 - 2. The lowest mean value was observed for the item chronic diseases on a scale of 0 - 1 and the mean value of 0.361.

The measure of the spread of data around the mean, standard deviation was assessed and the results are shown in table 4.2. For items in the scale of 1- 4, Item 6 had the highest standard deviation of 0.96 indicative of a varied data scores. The item with the least varied data was found to be item 15 (Length of therapy) with a standard deviation of 0.70. For items in the scale, 0 – 1, item 8 (Ventilator) was found to have a low standard deviation at 0.28, followed by item 2 (Chronic diseases) and item 11 (Healthcare acquired events) both with a standard deviation of 0.48 indicative of less varied data scores.

The results of the symmetric distribution of data were assessed by its skewness wherein, a perfectly normal distribution equal to zero (0) (Kim, 2013: 52). As seen in table 4.2, the following items: Severity of diseases, Combination antibiotics, microbiological results, Revision of therapy, and Patient’s outcome, had acceptable

skewness values for a normal distribution since their values were close to zero. Of the remaining items, 4 comprise negative skewness values indicating a departure from normality. Five items comprise positively skewed data indicative of values departing further from normality. Overall, 8 of the 13 items tested for skewness were non-normally distributed.

TABLE 4.2 DESCRIPTION OF THE EXTRACTED DATA OF ICU INPATIENTS (n = 59).

Variable	Scale	Mean	StDev	Variance	Skewness	Kurtosis
Severity of disease	1- 4	2,328	0,961	0,924	0,22	-0,85
Chronic diseases	0- 1	0,3607	0,4842	0,2344	0,6	-1,7
Ventilator	0- 1	0,918	0,2766	0,0765	-3,13	8,03
Clinical indication	1- 3	1,377	0,5821	0,3388	1,29	0,73
Combination antibiotics	0- 1	0,3934	0,4926	0,2426	0,45	-1,86
Microbiological specimen	0- 1	0,7541	0,4342	0,1885	-1,21	-0,55
Microbiological results	0- 2	1,131	0,785	0,616	-0,24	-1,33
Susceptibility results	0- 2	1,246	0,869	0,755	-0,51	-1,5
Revision of therapy	0- 2	0,967	0,93	0,866	0,07	-1,88
Length of treatment	1- 3	1,6066	0,6899	0,476	0,7	-0,62
Healthcare acquired events	0- 1	0,3443	0,4791	0,2295	0,67	-1,6
Length of stay	0- 4	1,459	0,697	0,4858	1,52	2,11
Patient's outcome	0- 1	0,4098	0,4959	0,2459	0,38	-1,92

The sharpness of the peak of the distribution of data was statistically measured by calculating the kurtosis value. The normality range for kurtosis is -3 to +3 (Ho & Yu 2014:371). The item ventilator demonstrated a high kurtosis value of 8.03 indicative of a distinct peak near the mean (Table 4.2). The rest of the items were within the kurtotic range indicative of a normal peak of the distribution of test scores.

4.4 QUESTIONNAIRE EVALUATION

According to William, Onsman and Brown (2010: 2) factor analysis is a multivariate statistical procedure involving two major classes of analytic approaches, the explorative factor analysis (EFA) that allows the researcher to explore the main dimensions to generate a theory or model from a relatively large set of latent constructs represented by a set of items, and confirmatory factor analysis (CFA) that allows the researcher to test a proposed theory or mode (William et al. 2012: 3). Seeing as the data collection tool was not entirely new and the hypothesis regarding the structural nature of the original factor was unknown, also it consisted of a lot of questions, some of which may measure different aspects of the same underlying variable, it was necessary to perform the EFA to uncover the underlying structure of the variable being measured and to analyse its internal reliability.

4.4.1 Inter-correlations

The first step in factor analysis entails the assessment of inter-correlations between the items studied, thus identifying the dimensionality of the correlation matrix by indicating variables that correlate highly with other variables (Field, 2000:424). The correlation results are shown in table 4.3. The largest correlation coefficient occurred between Item 7 (Microbiological results) and item 6 (Microbiological specimen) (r = 0.84), as well as between item 8 (Susceptibility results) and item 6 Microbiological specimen(r = 0. 83).

The following pairs of items had low correlations > 0.15: item 5 (Combination antibiotics) and item 2 (Chronic disease) (r= 0.09); Item 10 (Length of stay) and item 2 (Chronic disease) (r = 0.04); item 10 (Length of therapy) item 8 (Susceptibility results) (r = 0.09); item 11 (Healthcare acquired events) and item 2 (Chronic disease); item 11 (Healthcare acquired events) and item 8 (Susceptibility results) (r= 0.08); item 13 (Patient's outcome) and item 2 (Chronic disease) (r= 0.07); item 13 (Patient's outcome) and item 8 (Susceptibility results) (r= 0.07).

TABLE 4. 3 INTERCORRELATIONS AMONG THE STUDY VARIABLES (n = 59).

	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13
Item 1	1.00												
Item 2	.246	1.000											
Item 3	.446	.239	1.000										
Item 4	.351	.212	.245	1.000									
Item 5	.366	.093	.133	.242	1.000								
Item 6	.480	.127	**.325**	**.367**	**.377**	1.000							
Item7	.560	.110	.256	**.332**	**.363**	**.841**	1.000						
Item 8	.319	.193	.211	**.440**	**.339**	**.828**	**.540**	1.000					
Item 9	.530	.228	.264	.233	**.301**	**.573**	**.663**	**.445**	1.000				
Item 10	.207	.040	.312	.138	.102	.297	.232	.088	.264	1.00			
Item 11	.378	.045	.120	.034	.164	**.437**	**.811**	.068	**.492**	.081	1.000		
Item 12	.459	-.116	.316	.049	.194	**.441**	**.547**	.075	**.429**	**.414**	**.506**	1.000	.
Item 13	.366	.066	.081	.116	.387	**.307**	**.514**	.073	**.344**	.142	**.493**	.257	1.000

Since inter-item correlation examines the extent to which items on a scale are assessing the same construct, the low correlations may be due to the items not assessing the same construct. The results showed that not all items in the questionnaire were well correlated with each other, and therefore the questionnaire was possibly multidimensional. Furthermore, the negative correlations between items may imply that items may be worded in an opposite direction. Overall, the ASPAQ tool showed acceptable levels of consistency.

In the correlation matrix (table 4.3), 3 clusters of variables with high inter-correlations are bolded. These clusters could be suggestive of three possible factors. Item 6, 7,8 and 9 seem to load on one factor; item 11, 12 and 13 seem to load on another factor; and items 9, 10 and 11 load on another factor.

4.4.2 Bartlett’s test of sphericity

The inter-correlations of the items were further checked by using Bartlett's test of spherity for testing the null hypothesis that the correlation matrix is an identity matrix. When the correlation matrix is an identity matrix, this will indicate that the variables are unrelated and therefore unsuitable for factor analysis. The Bartlett's test gave a significant result of Chi-square = 488.917, p = 0.000, therefore signifying that a correlation between the variables exist and the correlation matrix is not an identity. The null hypothesis was rejected.

4.4.3 Sampling adequacy test

The adequacy of the sample for factor analysis was checked by using the Kaiser Meyer Olkin measure of sampling adequacy (KMO test) which specify that the sample will be deemed adequate if the value of KMO > 5 (Field, 2000: 446).

TABLE 4.4 KMO AND BARETT’S TEST RESULTS

Kaiser-Meyer-Olkin Measure of Sampling Adequacy.		.710
Bartlett's Test of Sphericity	Approx. Chi-Square	488.917
	df	78
	Sig.	.000

Factor analysis was considered appropriate for a further analysis of the data. Table 4.4 showed a KMO value of 0.710, which indicates that the sample is adequate to continue with factor analysis.

4.4.4 Total variance

For this study, the important factors are defined as those factors with an eigenvalue (variance) greater than 1. The first four factors have eigenvalues greater than 1 and explain most (69.19 %) of the variability in the data (Table 4.5).

TABLE 4. 5 EIGENVALUES AND TOTAL VARIANCE

Component	Initial Eigenvalues			Extraction Sums of Squared Loadings			Rotation Sums of Squared Loadings		
	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	4.998	38.449	38.449	4.998	38.449	38.449	3.076	23.662	23.662
2	1.648	12.674	51.123	1.648	12.674	51.123	2.647	20.362	44.024
3	1.280	9.845	60.968	1.280	9.845	60.968	1.921	14.777	58.801
4	1.069	8.221	69.189	1.069	8.221	69.189	1.350	10.388	69.189
5	.919	7.066	76.256						
6	.713	5.481	81.737						
7	.667	5.133	86.870						
8	.533	4.102	90.972						
9	.441	3.389	94.360						
10	.373	2.870	97.230						
11	.282	2.168	99.399						
12	.060	.459	99.858						
13	.019	.142	100.000						

Among the 13 components, component 1 accounts for the largest amount of variance 4. 998 (38.45 %) in the data, which means that out of the total variance, 38.45 % can be attributed to component 1. Component 2 is explained by 1.648 (12.67 %) of the amount of variability in the data. The third component (1.28) is explained by 9.85% and component 4 is explained by 1.069 (8.22 %) of the variability of the data. The remaining components, each explains less than 10 % of the variance of the data and may not be important enough to include in the further analysis.

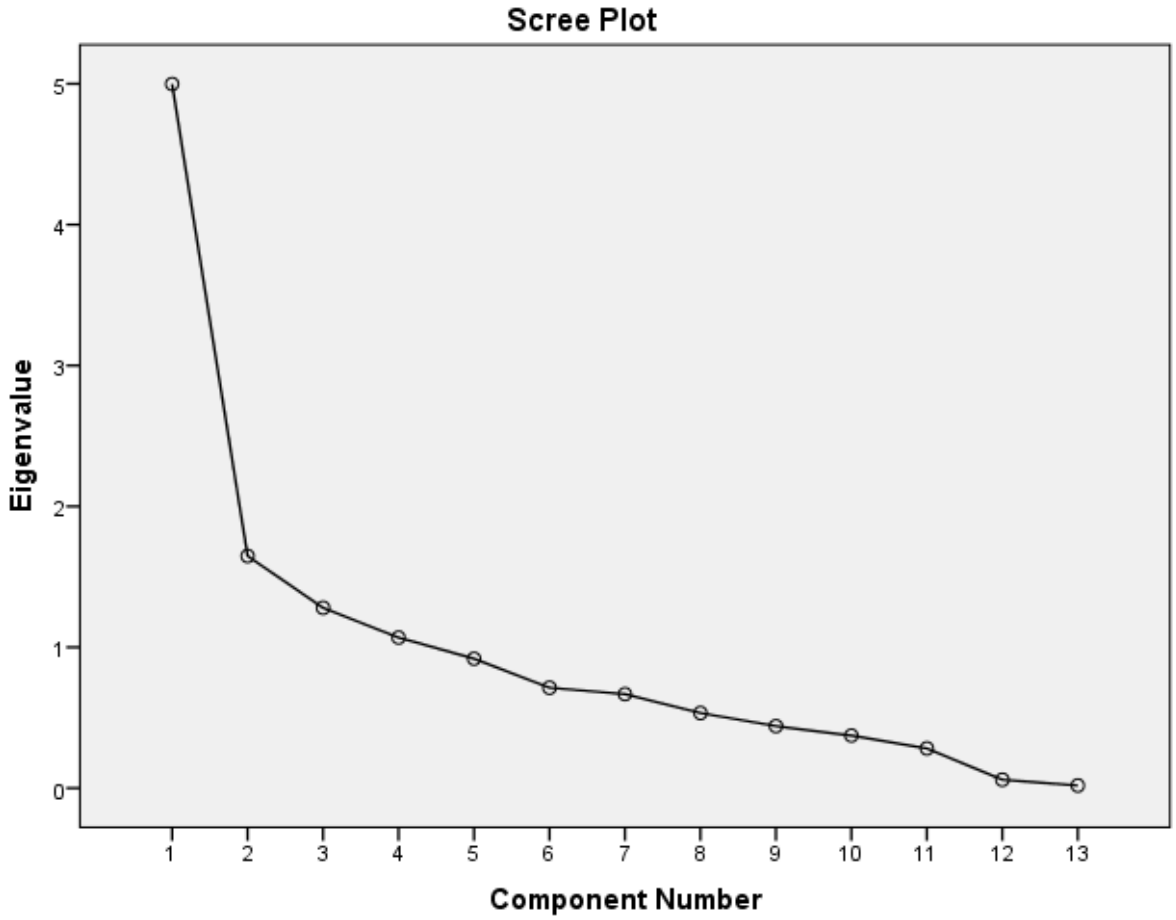


FIGURE 4.2 SCREE PLOT OF THE EIGENVALUES AGAINST THE DIFFERENT COMPONENTS

For visual determination of the number of factors to retain, the scree plot was used (Fig 4.2). The scree plot showed a distinct break between the steep slope of the large component and was the curve starts to flatten. The components with values above the point at which the curve flattens out, and had eigenvalues above 1 were retained. Furthermore, component 4 was excluded from the model because its eigenvalue barely exceeds 1 and explains less than 10 % of the total variance. Therefore, only three components were considered for this study.

4.4.5 Factor extraction

Communalities demonstrates how much of the variance in the variables have been accounted for by the extracted factors (Table 4.6). Among the 13 variables, communalities ranged from high of 0.921 for the item Microbiological results to a low

of 0.356 for the item Combination antibiotics variables. It can be said that all 13 variables, except for item Combination antibiotics had communality values above 0.5 and therefore all variables were included in the 3 selected factors. But only some of the variables had high loads within each factor. Overall 13 variables were reduced to 3 factors that accounted for 58.80 % of covariance among the variables.

Components were extracted using the principal component analysis method. Table 4.7 shows the results of the extracted components after Promax with normalization rotation was performed on the data. The table shows the loadings of each variable onto each factor. Loadings close to – 1 or 1 indicate that the factor strongly influences the variable, whereas loadings close to 0 indicate that the variable is weakly influenced by the factor.

TABLE 4.6 COMMUNALITIES VALUES BEFORE AND AFTER EXTRACTION

Variable	Initial	Extraction
Severity of the illness	1.000	.641
Chronic disease	1.000	.711
Ventilator	1.000	.664
Clinical indicator	1.000	.500
Combination antibiotics	1.000	.**356**
Microbiological specimen	1.000	.908
Microbiological results	1.000	.921
Susceptibility results	1.000	.913
Revision of therapy	1.000	.586
Length of therapy	1.000	.614
Healthcare acquired events	1.000	.785
Length of stay	1.000	.765
Patient's outcome	1.000	.629

All items had high loading values ≥ 5 with the exception of the item Combination antibiotics, this is indicative of the representativeness of the underlying factor. The communality value of the item Combination antibiotics was low indicating that the variable is an outlier. If an item is cross-loading (item loaded on two or more factors) it was placed in the factor with the highest factorial loading compared with the other

factors or to other factors due to theoretical reasoning. Four variables (Combination antibiotics, microbiological specimen, Length of stay, and Severity of illness) were found to have high factor loadings on different factors.

The following variables: Healthcare acquired events (0.980), Microbiological results (0.864), Patient's outcome (0.798), Revision of therapy (0.545) and Combination antibiotics (0.393) load primarily on factor 1. This factor explains the outcome of the patients with regards to developing hospital-acquired events, demonstrated in the microbiological test results and outcome of the patient. This factor has outcome measurements and is termed the Outcome factor.

TABLE 4.7 LOADING OF VARIABLES TO CORRESPONDING FACTORS.

	Component		
Item	1	2	3
Healthcare acquired events	**0,980448**		
Microbiological results	**0,863751**		
Patient's outcome	**0,798122**		
Revision of therapy	**0,544736**		
Combinatio antibiotics	**0,393051**		
Susceptibility results		**0,86431**	
Clinical indicator		**0,730628**	
Chronic disease		**0,546828**	
Microbiological results		**0,528479**	
Length of therapy			**0,801517**
Ventilator			**0,776247**
Length of stay			**0,554311**
Severity of illness			**0,348267**

The following items; Susceptibility results (0.864), Clinical indicator (0.731), Chronic disease (0.547) and Microbiological specimen (0.528) load primarily on factor 2. Factor 2 describes the effects of antimicrobials prescribed on the pathogen isolated from the collected patients' specimen, as well as the reasons for prescribing the

antimicrobials. This factor is therefore named the appropriate antimicrobial prescribing factor.

Factor 3 had a strong correlation with items; Length of therapy (0.802), Ventilator (0.776), Length of stay (0.554) and Severity of illness (0.348). It describes the influence of length of antimicrobials treatments, the use of mechanical ventilation and the severity of illness on the patients stay in a hospital. Therefore, this factor is named the risk factor.

This analysis revealed that the questionnaire was composed of three factors: patients' outcome, prudent antimicrobial prescribing and risk factors. The results show that the three factors are sub-components of ASPAQ. In addition, the intercorrelations among the factors were assessed (table 4.8). It can be seen that the factors 1 and factor 2 are correlated with r = 0.419, and factor 1 and factor 3 with r= 0.440, Factor 3 and factor have a borderline correlation with r= 0.29.

TABLE 4.8 COMPONENT CORRELATION MATRIX

Component	1	2	3
1	1,000	0,419	0,440
2	0,419	1,000	0,294
3	0,440	0,294	1,000

The internal consistency of the entire scale and the factors extracted was estimated using Cronbach's alpha coefficient (table 4.9). The reliability estimate for the entire scale was high (α = 0.83), signifying a high degree of homogeneity amongst the 13 items of the scale. The values of alphas were adequate with α = 0.80 for factor 1, α = 0.67 for Factor 2 and α = 0.74 for Factor 3, indicative of internal consistency within the items of each factor. To determine how each item individually contributes to the reliability of the entire scale, one item was deleted and the Cronbach's alpha re-estimated.

TABLE 4.9 THE ESTIMATED INTERNAL CONSISTENCY

Item	item -total correlation	Item deleted α values	Cronbach's alpha
Factor 1			**0.80**
Healthcare acquired events	0.54	0.82	
Microbiological results	0.91	0.78	
Patient's outcome	0.82	0.81	
Revision of therapy	0.78	0.80	
Combination antibiotics	0.70	0.82	
Factor 2			**0.67**
Susceptibility results	0.46	0.82	
Clinical indicator	0.67	0.83	
Chronic disease	0.80	0.84	
Microbiological specimen	0.89	0.84	
Factor 3			**0.74**
Length of treatment	0.49	0.84	
Ventilator	0.76	0.83	
Length of stay	0.78	0.82	
Severity of illness	0.60	0.81	
Entire test			**0.83**

From the results (Table 4.9) it can be seen that there was no difference between the alphas for item deleted and the alpha for the entire scale, indicating a positive contribution to the reliability of the scale.

4. 5 THE CAPACITY TO PRESCRIBE ANTIMICROBIALS

This section discusses the results of the capacity of the hospital to prescribe antimicrobials. The results of the capacity of the organisation to prescribe antimicrobials are presented in table 4.10. The total score of the capacity measure was found to be 69. 23 %, this is indicative of a sufficient capacity to prescribe quality antimicrobials. The deficiency of the capacity of the hospital to prescribe quality antimicrobials was observed for the core elements: leadership commitment (50.00 %).

Since leadership commitment ensures dedicated human, financial and information technology resources, a lack of support of facility administration to sustain an ASP in this institution was observed (Table 4.10) Chris Hani Baragwanath Academic Hospital established its ASP in 2016. It consisted of team members such as infection prevention and protection specialist, microbiology laboratory manager, clinicians and a pharmacist. Currently, the ASP is led by a pharmacist. This is expected because the ASP team should be led by a knowledgeable and respected leader with an extensive knowledge of antimicrobials and antimicrobial stewardship, who may be able to monitor antimicrobial use and make recommendations for treatment based on available guidelines.

TABLE 4.10 CAPACITY MEASURES OF ANTIMICROBIAL STEWARDSHIP PROGRAM

Key elements	**Yes**	**No**	**Total**	**Percent (%)**	**Characterized**
Leadership	1	1	2	50	Low
Accountability	1	0	1	100	Satisfactory
Drug expertise	5	2	7	71. 43	Sufficient
Action	11	6	17	64.70	Sufficient
Tracking	6	2	8	75.00	Sufficient
Reporting	2	1	3	66.67	Sufficient
Education	1	0	1	100	Satisfactory
Total	**27**	**12**	**39**	**69.23**	**Sufficient**

In this institution nurses were not included as the ASP team members, this was not expected as nurses are essential in monitoring and improving antimicrobial use through investigating changes in patients' condition, follow-up on microbiological results and adjusting antimicrobials accordingly. ASP members have other hospital duties and no dedicated time for ASP implementation, also the ASP had no formal funding and therefore depended on sponsors to support the ASP activities.

4.6 ANTIMICROBIALS PRESCRIBING

4.6.1 Appropriateness of antimicrobial selection

This section discusses the findings on the antimicrobial prescribing patterns in the ICU. The use of antibiotic prophylaxis before surgery has been found to significantly decrease surgical site infection and postoperative infections (Lundine, Nelson, Buckley, Putnis & Duffy, (2010: 367- 368). Almost 68 % of the patients were prescribed surgical prophylaxis, 17 (28.81%) were prescribed medical prophylaxis and only 2 (3.39 %) were prescribed therapeutic antimicrobials (Table 4.11). First-generation cephalosporin are the recommended first-line agents for most surgical procedures, targeting the most likely organism while avoiding broad-spectrum antimicrobial therapy that may lead to the development of antimicrobial resistance (Lundine et al.,2010: 368; Dellinger, Gross, Barrett, Krausse, Martone, McGowan, Sweet & Wenzel, 1994:423).

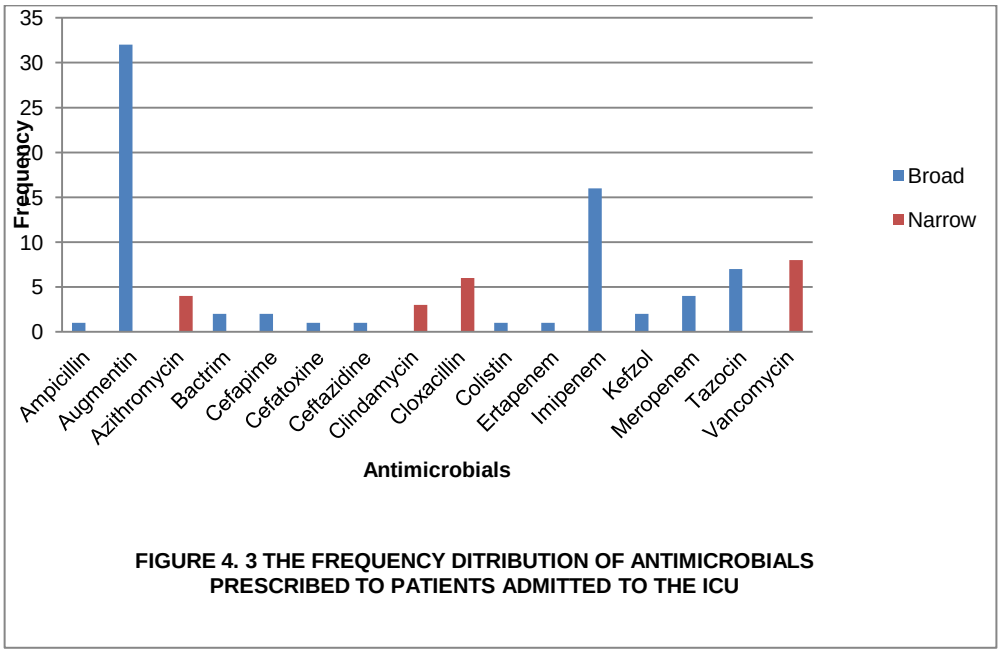


FIGURE 4. 3 THE FREQUENCY DITRIBUTION OF ANTIMICROBIALS PRESCRIBED TO PATIENTS ADMITTED TO THE ICU

In this study, the most common antimicrobials were augmentin which accounted for 35.16% of the total number of prescribed antimicrobials. Imipenem comprising 16 prescriptions was the second highest, followed by vancomycin 8 (8. 88%) then 7(7. 69%) of tazocin. Whereas, generation 3 cephalosporin: Cefatoxime and Ceftazidime

and generation 4 cephalosporin: Cefipime, cephalosporins were prescribed the least for only 4 cases, during the study period (Figure 4.3).

4. 6. 2 Antimicrobial spectrum

The majority of patients 51 (88.14%) were prescribed antimicrobials with a broad spectrum activity compared to 8 (11.86%) patients prescribed antimicrobials with a narrow spectrum (Table 4.6). The activity of the prescribed antimicrobials is shown in figure 4.2. The majority 70 (76.92%) of the prescribed antimicrobials were broad spectrum whereas, 21(23,08%) comprised of a narrow spectrum. According to Wasserman, Boyles and Mendelson, (2014:6) an appropriate empirical antibiotic can be selected by matching the narrowest spectrum antibiotic with the likely pathogen.

Out of 59 patients, 38 (64.41%) were prescribed a single antimicrobial, 16 (27.12 %) patients were prescribed 2 antimicrobials, and 5 (8.47%) were prescribed more than 2 antibiotics (Table 4.11).

4. 6.3 Appropriateness of antimicrobial therapy

During the follow-up of 59 participants, 44 (74.58 %) biological specimens were taken for culturing and a total of 23 (38.98%) biological samples were positive. Two patients were admitted because of the infections whereas, 21 developed hospital-acquired infections and all were prescribed antimicrobials (Table 4.1).

Of the 21 patients with HAI, 4 were treated with 3 or more antimicrobials, 7 were prescribed two antimicrobials and 10 were prescribed one antimicrobial as can be seen in table 4.12. In this study, the majority of prescribed antimicrobials were administered intravenously (IV) 57 (88.14%) and only 2 (3.39%) were administered orally (Table 4.11). This could be due to the severity of the condition of the patient and/or because the majority of patients were prescribed surgical prophylaxis. In addition, many patients in the ICU are unable to take anything by mouth due to intubation, scheduled medical procedure or an underlying condition.

TABLE 4.11 PATTERNS OF ANTIMICROBIAL PRESCRIBING IN THE ICU

PROCESSES	NUMBER OF PATIENTS	
	n	%
INDICATION OF TREATMENT		
Medical prophylaxis	16	27. 12
Surgical prophylaxis	40	67. 80
Therapeutic	3	5. 08
MICROBIOLOGICAL LABORATORY RESULTS		
Positive	23	38. 98
No growth	21	35. 59
Not tested	15	25. 42
SPECTRUM OF ANTIMICROBIAL		
Broad	51	88. 14
Narrow	8	11. 86
NUMBER OF ANTIMICROBIALS		
1	38	64. 41
2	16	27. 12
>2	5	8.47
DURATION OF THE TREATMENT (Mean ± Sd; 4.17 ± 1.84)		
1 - 3 days	31	52. 54
4 - 6 days	20	33. 90
7 - 9 days	8	13. 56
ADMINISTRATION OF THERAPY		
IV	57	96. 61
Oral	2	3. 39

Although, the use of a combination antimicrobial therapy is discouraged, in this study, it was found that the combination therapy was used for the synergistic and extension of activity of the antimicrobials and for the prevention of the development of resistance (Wasserman et al., 2014: 9)

TABLE 4.12 NUMBER OF ANTIMICROBIALS PRESCRIBED FOR PATIENTS WITH HAI (n= 40).

Number of antimicrobials	**Number of patients**	
	n	%
1	10	47.62
2	7	33. 33
≥ 3	4	19. 05

The judgement of the appropriateness of antimicrobials per patient showed that 4 (19.05 %) of the 21 patients with HAI were prescribed inappropriate antimicrobials.

TABLE 4. 13 ASSESSMENT OF ANTIMICROBIAL THERAPY

	Antimicrobial selection	Antimicrobial dosages	Antimicrobial administration	Duration of therapy
Appropriate	18 (92.11 %)	20 (97.37 %)	21 (100%)	21 (100%)
Inappropriate	3 (7. 89 %)	1 (2. 63 %)	0	0
Total	21	21	21	21

In 3 (14.29 %) patients, the choice of the agents were not according to the guidelines, whereas, the antimicrobial dosage prescribed for 1 (4.76 %) patient was not according to the guidelines and therefore considered inappropriate as shown in table 4.13. The route of administration and the duration of antimicrobials treatment were appropriate in all patients.

4.7 INCIDENCE OF DIFFERENT BACTERIA IN THE ICU

TABLE 4.14 FREQUENCIES AND SUSCEPTIBILITY OF BACTERIAL SPECIES ISOLATED FROM MICROBIOLOGICAL SAMPLES AMONGST ICU INPATIENTS (n= 27).

Pathogen	Resistant		Sensitive		Total	
	n	%	n	%	n	%
A baumannii	4	14.81	-	-	4	14.81
C difficile	-	-	1	3.70	1	3.70
Clostridium spp.	-	-	2	7.41	2	7.41
Corynbacter	1	3.70	-	-	1	3.70
E coli	2	7.41	2	7.41	4	14.81
E faecium	1	3.70	-	-	1	3.70
Enterobacteria spp.	2	7.41	-	-	2	7.41
H influenza	1	3.70	-	-	1	3.70
Klebsiela	1	3.70	-	-	1	3.70
S aureus	4	14.81	2	7.41	6	22.22
S pneumoniae	2	7.41	1	3.70	3	11.11
Salmonela spp.	1	3.70	-	-	1	3.70
Total	19	70.37	8	29.63	27	

This section dealt with the results of the assessment of the incidence of hospital acquires infections and the identification of the risk factors. Table 4.14 shows the frequencies of pathogens isolated from microbiological samples of ICU admitted patients.

TABLE 4.15 THE INCIDENCE RATES OF HAI AMONGST ICU INPATIENTS (n = 42).

Charecteristics	Negative n= 21 (50.00 %)	Positive n= 21 (50.00 %)	Incident rate (%)
Gender			
Male	15 (35.71 %)	10 (23.81 %)	23.81
Female	6 (14.28 %)	11 (26.19 %)	26.19
Age			
19 - 38	12 (28.57 %)	13 (30.95 %)	30.95
39 - 58	5 (11.90 %)	6 (14. 28 %)	14.28
59 - 78	3 (7.14 %)	2 (4. 76 %)	4.76
79 - 98	1 (2.38 %)	0	-
Race			
Blacks	16 (38.09 %)	17 (40.48 %)	40.48
Coloureds	1 (2.38 %)	1 (2. 38 %)	2.38
Indians	2 (4. 76 %)	0	-
Whites	2 (4. 76 %)	3 (7. 14 %)	7. 14
Diagnosis groups			
Circulatory system	2 (4.76 %)	0	-
Digestive system	5 (11.90 %)	1 (2. 38 %)	2.38
Endocrine, nutrition and metabolism	0	3 (7.14 %)	7. 14
Genitourinary system	0	2 (4.76 %)	4. 76
Respiratory system	2 (4.76 %)	3 (7.14 %)	7. 14
Trauma	12 (28.57%)	12 (28.57%)	28. 57
SOI			
Minor	5 (11.90 %)	1 (2. 38 %)	2. 38
Moderate	8 (19.04 %)	7 (16. 67 %)	16. 67
Major	7 (16. 67 %)	8 (19. 04 %)	19. 04
Catastrophic	1 (2.38 %)	5 (11. 90 %)	11. 90
Chronic disease			
Present	8 (19.04 %)	8 (19.04 %)	19.04
Absent	13 (30.95 %)	13 (30.95 %)	30. 95
Mechanical ventilation			
Present	20 (47.61 %)	20 (47.61%)	47. 61
Absent	1 (2.38 %)	1 (2.38 %)	2. 38

Twenty seven pathogens were isolated from the 21 patients diagnosed with HAI. The most frequent bacterial species isolated was *S aureus* (n = 6; 22.22 %) followed by *E coli* (n = 4; 14.81 %) and *A baumannii* (n = 4; 14.81 %) followed by S pnuemoniae (n = 3, 11.11 %). Corynbacter, *E faecium*, *H influenza, Klebsiela, C difficile* and *Salmonela* species were the least frequently isolated pathogens, all had single (3.70 %) isolates. From the 27 isolated pathogens, 19 (70.37 %) were resistant to the prescribed antimicrobials. All 4 (14.81 %) *A baumannii* isolates were resistant, 4

(66.67 %) of the *S aureus* were also resistant and 50% of *E coli* isolates were resistant.

Table 4.15 shows the results of the incidence of hospital-acquired infections. From a total of 42 patients tested for HAI, 21 (50.00 %) patients had positive microbiological samples. Of the total 59 participating patients 21 (35.59 %) developed HAI but from 59 patients only 44 microbiological samples were tested.

The positive microbiological samples were from 11 (25.00%) female patients and 10 (27.27%) from male patients. Female patients had the highest incidence rate (26.19 %) of hospital-acquired infection than male patients (23.81 %). Patients of the age group 19 – 38 years had the highest rate (30.95 %) of developing hospital-acquired infections during this study. Black patients had the highest incidence rate (40.48 %) compared to other races. This result was expected as most of the patients 48 (81.36 %) were blacks (Refer to table 4.1). Patients admitted with trauma and those with major illnesses showed high incidence rates of 19.04 % and 28.57 % respectively.

TABLE 4.16 THE ASSOCIATION BETWEEN POSSIBLE RISK FACTORS AND HIA (n = 42)

Item	**X^2 - value**	**df**	**Critical χ^2 value**	**p-value**
Age	1.34	3	7.82	0.72
Gender	2.75	1	3.84	0.10
Race	2.24	3	7.82	0.52
Diagnosis groups	9.86	5	11.07	0.08
Clinical indication	1.06	2	5.99	0.59
Severity of illness	5.40	3	7.82	0.14

The univariate analysis of risk factors for developing HAI showed that all risk factors studied (Age, gender, race, diagnostic groupings, clinical indications and severity of the illness) were not significantly associated with hospital-acquired infection $p< 0.05$ (Table 4.16). The Chi-square critical values were found to be greater than the

calculated Chi-square implying that the null hypothesis that states that: there is no association between possible risks factors and the incidence of HAI in the ICU was accepted (Table 4.16).

4.8 IMPACT OF ANTIMICROBIAL STEWARDSHIP PROGRAM

This section deals with the evaluation of the effectiveness of the antimicrobial stewardship program with respect to improving the quality of antimicrobial prescribing. The impact of ASP was assessed through the identification of five core evaluation elements: reach, effectiveness, adoption, implementation, and maintenance.

4.8.1 Reach dimension

Regarding the demographics of the participants, the total of 65 participants was recruited for the study but 3 (4.62 %) declined and 3 (4.62 %) participants were missing data, such that only 59 (90.77 %) patients participated in the study (refer to table 4.1). The participants comprised 33 (55.93 %) male and 26 (44.07 %) female patients (Fig 4. 4).

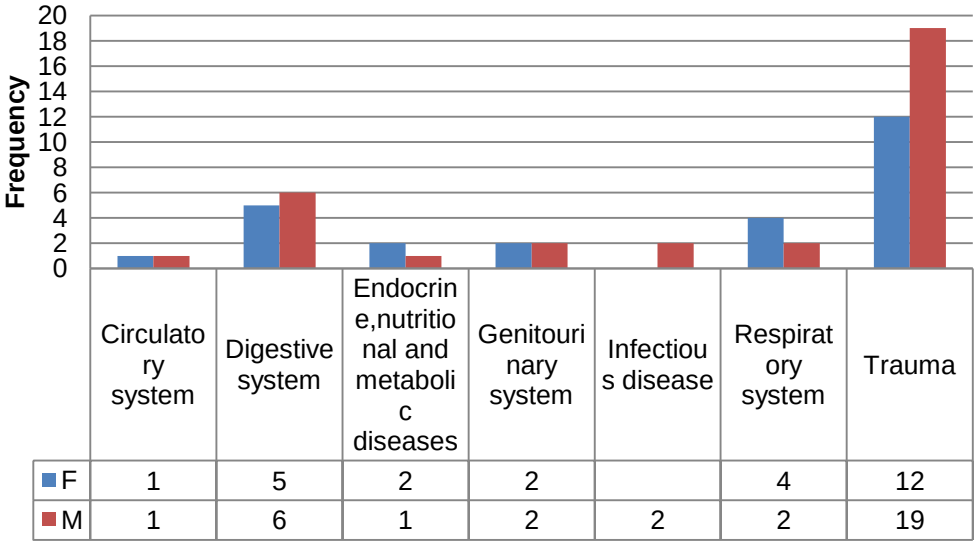


FIGURE 4.4 DISTRIBUTION OF PATIENTS ACCORDING TO DIAGNOSIS GROUPS

Most participants 34 (57.63 %) were in the age group 19 - 38 years and those who were 59 or older accounted for a small proportion (13.55 %) of the participants. The participants' race was categorised as Black, White, Indian and Coloured, and the majority were Blacks (n = 8; 81. 36 %) followed by Whites (n = 6; 10.17 %). Indian patients accounted for a smaller proportion (3.38 %) of the participants.

4.8.2 Effectiveness dimension

Of the 59 participants, the majority (n = 27; 45.76 %) had moderate illnesses followed by 13 (22.03 %) with minor illnesses. Catastrophically ill participants accounted for a smaller proportion (n-6; 10. 10 %). Fifteen (25.42 %) patients were not tested for microbiological cultures, 23 (38.98 %) patients had positive microbiological cultures and 21(35.59 %) participants had negative microbiological cultures (Fig 4.5). Of the 23 positive microbiological specimens, 2 (8. 70 %) were admitted for infectious diseases whereas, 21 (91.30 %) developed infections in the hospital (Fig 4.5).

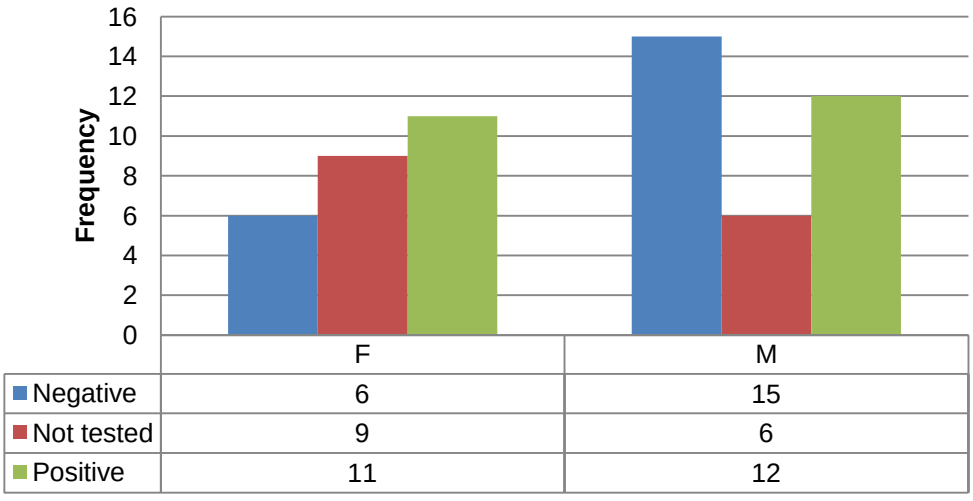
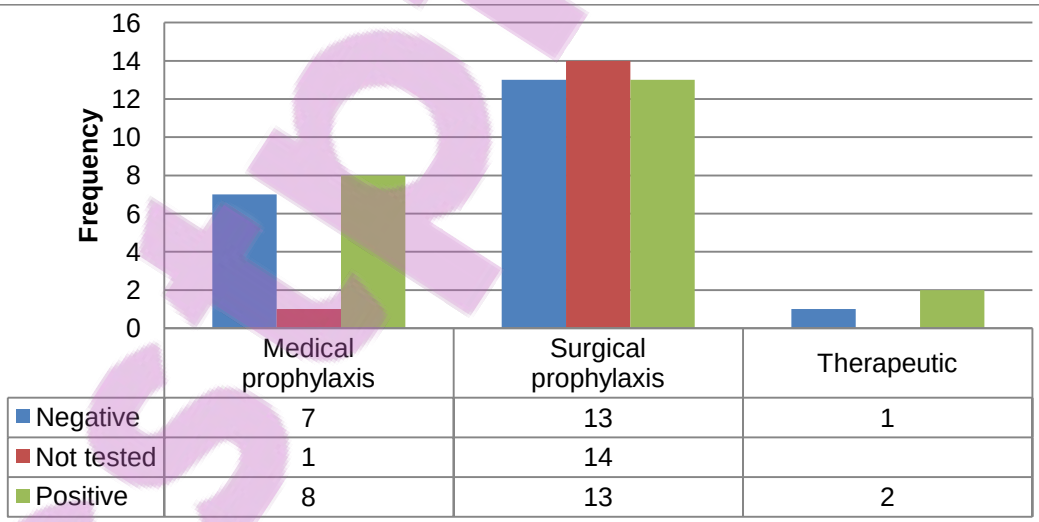


FIGURE 4.5 MICROBIOLOGICAL TEST RESULTS OF PATIENTS ADMITTED TO THE ICU

Regarding the safety of care, 21 (35. 59 %) participants developed hospital-acquired infections (Table 4.11). Eleven (18.64 %) of the HAI positive patients were females

whereas, 10 (16.95 %) were males. Among the studied races, 17 (28.81 %) Blacks, followed by 3 (5.08 %), then Coloured 1(1. 69 %) tested positive for HAI. Of the total 59 participants, 12(20.33 %) diagnosed with trauma, 3 (5.08 %) diagnosed with the diseases of endocrine, nutrition and metabolism and 3 (5. 08 %) diagnosed with the diseases of the respiratory system tested positive for HAI. Eight (13.56 %) who had major illnesses, 7 (11.86 %) patients with moderate illnesses and 5 (8.47 %) patients with catastrophic illnesses all, tested positive for HAI.

Regarding the quality of care, participants were prescribed antimicrobials for different reasons (Figure 4.6). Sixteen (27. 12 %) participants were prescribed antimicrobials for medical prophylaxis, 40 (67.80 %) were prescribed antimicrobials for surgical prophylaxis and 3 (5.08 %) participants were prescribed antimicrobials for therapeutic reasons. Of the participants prescribed medical prophylaxis, 8 (50.00 %) participants tested positive for HAI whereas, 13 (32.50 %) patients prescribed surgical prophylaxis tested positive for HAI. In total, the number of patients tested positive for HAI were 21 (35. 59 %). The 14 (23.73 %) patients treated with surgical prophylaxis were not tested, suggesting that no signs of infection were observed and therefore, the preventive treatment was successful.



	Medical prophylaxis	Surgical prophylaxis	Therapeutic
Negative	7	13	1
Not tested	1	14	
Positive	8	13	2

FIGURE 4.6 MICROBIOLOGICAL TEST RESULTS ACCORDING TO DIFFERENT ANTIMICROBIAL INDICATIONS

Refer to table 4.13, of the 21 HAI positive participants, 3 (14.29 %) were prescribed inappropriate antimicrobials due to the wrong selection of the antimicrobials. A single (4.76 %) patient was also prescribed inappropriate antimicrobial, but due to the wrong dosage. In total 4 (6.78 %) patients out of 59 participants were prescribed inappropriate antimicrobials. Seventeen (80.95 %) patients were prescribed appropriate antimicrobials.

4.8.3 Adoption dimension

The results for the adoption dimension are shown in table 4. From 8 academic hospitals situated in Gauteng Province, two healthcare institutions were recruited for the study. Of the 2 recruited hospital only one (50.00 %) participated.

4.8.4 Implementation dimension

Regarding the staff willing to implement the program, of 6 trained and educated multidisciplinary ASP members recommended, 5(83.33 %) antimicrobial stewardship members including infection prevention and protection physician; microbiological laboratory specialist (leader); clinicians with an interest in infection, pharmacist with expertise in infection were identified with the exception of nurses staff (16.67 %).

Regarding the list of essential antimicrobials, both essential medicine list and evidence-based local antimicrobial guidelines were available (100%). The microbiological laboratory is situated in the enclosure of the healthcare facility for timely reporting of the results. Implementation dimension measures the extent to which different components of the program are delivered as intended which were evaluated using the principles for rational antibiotic prescribing (Wasserman et al. 2014: 6-10).

TABLE 4. 17 PROCESSES OF QUALITY ANTIMICROBIAL PRESCRIBING.

Process	**Performed**	**Skipped**
Indication for antimicrobial use	X	
Obtain cultures	X	
Antimicrobial choice:		
Target the most likely pathogen	X	
Assess the likelihood of resistance	X	
Review contraindication (allergy)		X
Select antimicrobial with adequate tissue penetration	X	
Aim for a single antimicrobial with the desired spectrum	X	
Appropriate antimicrobial dosage	X	
Appropriate dose frequency	X	
Appropriate route	X	
Therapeutic drug monitoring		X
The desired spectrum covered	X	
De-escalation:		
Route		X
Spectrum		X
Total	10 (71.43 %)	4 (28.57 %)

Refer to table 4.17, the majority 10 (71.43 %) of the steps for prescribing quality antimicrobials were delivered as intended with the exception of 4 (28.57 %). The results are surprising since prescribing an antimicrobial without testing for allergies can aggravate the condition of the patient and endanger the patient's life. Since the the route and spectrum of the prescribed antimicrobial for patients in the ICU were not changed because the administration of an antimicrobial depends on the site and severity of the infection and is governed by the dosage (Baggot,1998:179). Most 57(96.61 %) patients were administered antimicrobials intravenously (IV) (Table 4.11).

Furthermore, Baggot (1998:178) noted that oral administration is used in the treatment of mild and moderate infections or when a prolonged duration of therapy is anticipated. Therefore, the IV route of administration chosen can be due to the

condition of the patient or the severity of the infection and mostly the intended quick eradication of the infection.

Table 4.18 shows the performance measures of ASP for each RE-AIM dimensions except the maintenance dimension. The maintenance dimension could not be considered for this study because the data collection only took 3 months whereas, the long-term effects of the program are meant to be measured after >6 months. For the reach dimension, a high-performance rate of 90.80 % was observed.

TABLE 4. 18 IMPACT MEASURES OF RE-AIM DIMENSIONS

RE-AIM dimension	Measure	Performance scores	Performance rate
Reach	Number of participants.	0.908	90.80 % **90.80 %**
Effectiveness	Patients without HAI.	0.644	64.4 % **64.4 %**
Adoption	Number of participating institutions. Number of ASP team members. In-house laboratory Antimicrobial guidelines and essential list **MEAN**	0.500 0.833 1 1	50. 00% 83.3 % 100 % 100 % **83.33 %**
Implementation	Extent of the processes of quality antimicrobial prescribing	0.714	71.43 % **71.43 %**
Average			**77.49 %**

For effectiveness dimension, the program performed fairly with 64.40 % of patients not developing HAI, indicating a success rate of preventing the development of HAI. The total rate of effectiveness was fair at 64.40 %. The antimicrobial stewardship program in the studied facility was highly adopted at the adoption rate of 83.33 %, the facility had an in-house microbiological laboratory and the list of essential antimicrobials including the antimicrobial guidelines. In the hospital studied 71.43 %

of the steps recommended for prescribing quality and effective antimicrobials were successfully followed and therefore, the implementation rate of the ASP in the hospital was good enough.

4.10 CONCLUSION

This chapter discussed the findings of this study with reference to 5 research questions. Three latent variables that explained the correlation between the observed variables were identified using a principal component analysis and Promax with Kaiser Normalisation rotation. These factors correlated with each other. Alphas for the entire scale and Factors showed internal consistency within the items.

The capacity of the participating hospital to prescribe quality antimicrobials was found sufficient in this study. The majority of patients admitted in the ICU were prescribed quality antimicrobials whereas; only 4 patients were prescribed inappropriate antimicrobials according to the guidelines. Forty-two bacterial species were isolated from biological sampled obtained from patients admitted in the ICU. Both male and female patients were equally infected but had different frequencies for different pathogens. The incidence of HAI in the ICU was moderate and more frequent for the age group 19 – 38 years. In addition, black patients and patients with major illnesses were frequently infected in the ICU. All possible risk factor for the development of HAI and assessed in this study were not risk factors

Although, the effectiveness of the ASP was average, the overall impact of ASP to prescribe quality antimicrobials was high. The leadership support for ASP's effort of promoting prudent prescribing of antimicrobials was low. It was identified as the weakness of the capacity performance of the hospital and a number of strategies were recommended to strengthen and improve the weakness.

In the next chapter, the implications of the findings for the participating hospital, the impact of ASP on the development of hospital-acquired infection and the evaluation of the programs impact using RE-AIM framework will be discussed. The limitations of this study will also be discussed and recommendations made.

CHAPTER 5

SUMMARY AND DISCUSSION

5.1 INTRODUCTION

This chapter provides a summary of the study, including the purpose of the study and the discussion of the main findings. A detailed summary of the study, including literature review and methodology as well as the findings of the study will be discussion herein.

5.2 SUMMARY OF THE STUDY

The current study aimed at assessing the effectiveness of antimicrobial stewardship program in limiting the spread of antimicrobial resistance in the hospital's ICU. It also aimed at identifying the deficiencies in the program's performance and proposing strategies for strengthening these deficiencies.

The threat posed by antimicrobial resistance has become a global issue, particularly in the ICU due to the increasing rates of inappropriate antimicrobial prescribing associated with greater morbidity and mortality (Llor & Bjerrum, 2014: 229; Kollef & Micek 2012: 179). Thirty to 60% of antimicrobials prescribed in the ICU are either unnecessary, inappropriate or suboptimal (Luyt, Brechot, Trouillet & Chastre 2014: 480). The development of resistance can delay the prescribing of quality antimicrobial treatment for the infection, thus aggravating the condition of the patient and leading to the extension of the hospital stay (Brink et al. 2006: 153). Consequently, a well structured hospital-based antimicrobial stewardship may afford the best care of patients with infection and prevent the development of resistant bacteria (Leuthner & Doern 2013: 3919). A multifaceted approach: antimicrobial stewardship program, aimed at increasing clinical outcomes, minimize adverse effects of antimicrobial use and reduce healthcare costs by improving antimicrobial use was introduced (Dellit et al. 2007: 159). This approach has been shown to impact the emergence of antimicrobial resistant bacteria by optimising the treatment of infections and reducing adverse events associated with antibiotic use (Davey et al. 2013: 15).

The evidence of high rates of antimicrobial resistance from published literature has highlighted the importance of investigating the effectiveness of antimicrobial stewardship program implemented in the South African hospital. Therefore, this study focused on evaluating the efficacy of ASP that has been implemented and is in operation in the Chris Hani Baragwanath Academic Hospital in the Gauteng Province.

5.3 STUDY DESIGN AND SETTING

A quantitative, single group before- and –after quasi-experimental design was conducted to evaluate the impact of ASP on reducing the development of antimicrobial resistant in the ICU by improving the quality of the prescribed antimicrobials (Kothari 2004:41). This was the appropriate method to use because the data collected was in numerical form and was analysed using a statistical procedures, also, as the study used critically ill patients, it was not logistically feasible or ethical to conduct a randomized controlled trial of causal research design and thus no group was allocated as a control (Harris, Bradham, Baumgarten, Zuckerman, Fink & Perencevich 2004:1586-1587). The study was conducted in the intensive care unit and as such, by using this method the existing setting was not disrupted. The study was conducted at the Chris Hani Baragwanath Academic Hospital in South Africa, Gauteng Province.

The study population included all critically ill patients, 18 years and older, admitted to the ICU during the period of data collection. Patients also had to be admitted in the ICU for 48h or more with no signs of bacterial colonisation and prescribed antimicrobials, to be included. Sixty-five patients were approach for participation in the study, of which 3 denied to participate and another 3 had incomplete information extracted from their records. The total number of patients who participated in this study was 59.

A structured questionnaire was used to collect information from the patients' medical records. All the data were de-identified and participants were given a study number. Extracted data was entered into the SPSS computer program and analysed.

5.4 SUMMARY OF THE RESULTS

5.4.1 Validation of the measuring instrument

This study has validated a vaguely new antimicrobial stewardship program assessment questionnaire. Factor analysis technique through principal component analysis and Promax rotation was used. Three factors were highlighted and explained 58.8 % of the measurement variance. Factor 1, the outcome factor, grouped items that measure the clinical outcomes related to antimicrobial use and the common adverse effects thereof. This factor explained 38.45 % of the measurement variance. Factor 2, appropriate antimicrobial prescribing factor, grouped items that measure the quality of antimicrobial prescribing through the assessment of the selection of the ideal antimicrobial drug regimen, dose, duration and the route of administration. This factor explained 12.67% proportion. Factor 3, risk factors, explained 9.84 % proportion of the measurement variance. This factor grouped items that are related to the appropriateness and duration of treatment, the severity of the illness and also the length of stay that may have an impact on the development of antimicrobial resistance.

Each item of the ASPAQ tool demonstrated high loading values (≥ 0.5) indicative of a valid measurement tool. In addition, the Cronbach's alpha for the entire scale was high (α = 0.83), indicating a strong relationship between the concepts represented by each factor. For the assessment of the strength of factors underlying the dataset the Cronbach's alphas of Factor 1 (outcome factor) α = 0.80 and Factor 3 (α = 0.74) demonstrated strong factors underlying the dataset, whereas the strength of Factor 2 (α = 0.67) was adequate. The correlations between the entire scale and the item score were moderate to high: alpha ranged from 0.46 to 0.91. In addition, all items contributed positively to the reliability of the total scale except the item microbial test results (α = 0.78) which resulted in a low α- value after deletion compared to the entire scale (α = 0.83). After deletion of the remaining items, no changes were observed. The evaluated questionnaire was considered reliable.

5.4.2 Research question 1

Does the hospital have the capacity to appropriately prescribe antimicrobial?

The capacity of the hospital to prescribe quality antimicrobials was assessed by identifying the core elements of hospital antibiotic stewardship program available in the hospital. The findings of this question revealed that leadership support was lacking in the hospital. Leadership commitment ensures dedicated human, financial and information technology resources (CDC 2014: 4). Although Abbo, Smith, Pereyra, Wyckoff, and Hooton (2012: 376) encourages the inclusion of nurses in the antimicrobial stewardship program to improve the effective use of antimicrobials, in this study, it was found that nurses were not represented in the ASP team of the studied institution. Edwards, Drumright Kieman, and Homes (2011: 6) indicated that nurses are best positioned to monitor and audit prescriptions but their role in ASPs is often overlooked.

Furthermore, ASP team members in this institution have other hospital duties and therefore could not dedicate their time entirely to the ASP but incorporate their ASP work into existing duties. The ASP team need to be allocated more time to contribute to the running of the antimicrobial stewardship program.

The ASP had no formal funding such that the institution depended on sponsors to support the ASP activities, with the hope that in the long run, the ASP may become self-sufficient by preventing expenditures on unnecessary antibiotics and prevention of the development of resistant pathogens.

5.4.3 Research question 2

How appropriate are the antimicrobial prescribing procedures to patients suspected to have hospital-acquired infection 48 –72 h after admission?

The findings of this study revealed that less than 20 % of patients who developed hospital-acquired infections were inappropriately prescribed antimicrobials. Contrary to the findings of this study, the study by Baktygul et al. (2011: 165) found that 73.3% of patients were prescribed inappropriate antimicrobial therapy. This was also evident in a study by Adorka, Mitonga, Lubbe, Serfontein and Allen (2014:356).

According to Willemsen, der Kooij, van Benthem, Wille and Kluytmans (2010: 6) judging the appropriateness of the antimicrobial therapy is not easy and requires extensive training. In addition, insufficient patient information complicates the judging of the appropriateness of antimicrobial therapies (Willemsen et al. 2010: 6). In this

study, all of the prescribed antimicrobials were assessed for appropriateness, but the results may be an underestimation of the potential inappropriate prescribing of antimicrobials. Therefore, validation of the results by expects may probably adjust the findings downwards.

5.4.4 Research question 3

What is the incidence of different disease-causing bacteria and antimicrobial susceptibility patterns in patients in the ICU?

The results showed a high incidence rate of HAI (50%) that is slightly above the rate reported for Sub-Saharan Africa hospital-acquired infection which ranged from 2 – 49% (Mbim, Mboto & Agbo 2016: 3). Furthermore, the high HAI rate in this study was corroborated by the EPIC II study, which reported the rate of all infections as 51% (Vincent, Rello, Marshall, Silva, Anzueto, Martin, Moreno, Lipman, Gomersall, Sakr & Reinhart 2009: 2327). Yesilbag, Karadeniz, Basaran and Kaya (2015: 236) reported the rate of nosocomial infection as 65 %, higher compared to the infection rate found in this institution. According to Khan, Baig and Mehboob (2017: 478), an increase in these infections may lead to an extended stay in the hospital, increased morbidity, increased antimicrobial resistance and increased mortality rate.

The frequently isolated bacteria in this study included *S aureus*, *E coli, A baumannii* and *S pnuemoniae,* which are considered the main pathogens associated with hospital-acquired infections, apart from *S pnuemoniae* (Lisboa & Nages 2011: 120). These pathogens are referred to by the acronym ESKAPE, they account for more than 80 % of infectious episodes in the ICU and involves both gram-negative and gram-positive bacterial species, which are characterized by increasing levels of antimicrobial resistance (Santajit & Indrawattana 2016: 1; Zilahi, Artigas & Martin-Loeches 2016: 97). These infections are the most common complications affecting hospitalized patients (Mishra, Panarjee & Gosain 2014: 39). In their study, Yesisbag et al. (2015: 236) found that *K pneumonia*, *P aeruginosa*, *Acinetobacter spp*. and *E coli* were the most common pathogens, which was contrary to the findings of this study. In addition, the frequency of *S aureus* infections was low (4%) compared to the 14.81 % frequency found in this study. The growing numbers of ESKAPE pathogens place a significant burden on healthcare systems (Santajit & Indrawattana 2016: 1).

The high incidence rates observed in this study indicate that the antimicrobial stewardship program implemented in this facility was not effective in improving the safety and care of the patients, one of the program's main objectives. To minimize the incidence and adverse outcomes of these infections, appropriate resources and activities to protect patients, healthcare workers and visitors from infections are essential, and these should be accomplished in the most cost-effective manner (Misra et al. 2014: 38).

Certain factors can affect the development of hospital-acquired infections: these include the underlying disease process as well as the severity of the disease (Mishra et al. 2014: 39); invasive devices such as mechanical ventilators and urinary catheter; surgical interventions applied, which may be an entrance for the causative microorganisms (Yesilbag et al. 2015:237). Furthermore, Weinstein (1998: 417) stated that nosocomial infections typically affect patients, who are immunocompromised because of age, underlying diseases, or medical or surgical treatment.

The univariate analysis revealed that age, gender, use of mechanical ventilation, the severity of illness and diagnostic groupings were not significantly associated with the development of HAI in this study. Contrary to the study by Yesilbag et al. (2015: 237) that revealed that the use of mechanical ventilation, hemodialysis, central vascular line, urinary catheter, nasogastric catheter were significantly associated with an incidence of HAI. Their findings further showed no significant correlation between age and the development of HAI, which was in line with the findings of this study (Yesilbag et al. 2015:237). This finding was also corroborated by the study of Mihaly, Orsolya, Monica, Anna, Hajna, Maria and Judit (2016: 307) which found no significant differences between infected and non-infected patients regarding age and gender.

In this study, factors such as old age, underlying diseases, the severity of the illness and undergoing surgical procedures did not significantly increase the chances of more patient developing HAI, moreover, there are contradictions observed in published data as discussed above.

5.4.5 Research question 4

How effective are current antimicrobial stewardship programmes in improving the quality of antimicrobial prescribing in the ICU?

In order to address this research question, the RE-AIM framework was adapted (Glasgow et al. 1999:1322). This framework focuses on five most important dimensions (Reach, Effectiveness, Adoption, Implementation and Maintenance) for evaluating the potential public health impact of programs intended for wide-scale implementation and dissemination (Compernolle, De Cocker, Lakeveld, Mackenbach,Nijpels, Oppert, Rutter, Teixeira, Cardon & Bourdeaudhuij 2014: 149). The RE-AIM framework has been widely used in international studies (Baba, Oliviera, Silva, Vieira, Cerri, Florindo & Gomes 2017: 709; Compernello et al. 2014:147; Farris, Will, Khavjou & Finkelstein 2007: 641; Jaurequi, Pacheco, Soltero, O'Connor, Castro, Estabrooks, McNeil & Lee 2015:162; King et al., 2010: 2076; Sweet et al. 2014: 74). Thus far this is the first study to evaluate the impact of health promotion program using the RE-AIM framework in the ICU.

The RE-AIM evaluation revealed that the program reached approximately 90 % eligible critically ill adult patients admitted in the ICU. This was calculated as the percentage of the number of participants divided by the number of eligible and invited people (Compernolle et al. 2014:49). Considering study group differences, reach was substantially greater for the Black patients than other race groups. According to Soto, Martin and Gong (2013: 3183) men and African Americans have a higher incidence of getting critically ill and admitted to the ICU. Whereas, the general household survey conducted by Statistics South Africa (Lehohla 2013:77) found that most people from white population group were reported ill or injured before the survey than people from black African and Coloured population groups. However, most Blacks and Coloureds use public health facilities whereas; most of the Whites and Indians population groups use private health facilities (Lehohla 2013: 17). Accordingly, small numbers of Whites and Indian are observed in public hospitals, such as the one studied herein.

Regarding the age difference, most patients reached were younger than 65 years compared to the elderly patient group, this was a surprise finding. Solis-Vernadez, Vilades-Reyes, Garza-Gonzalez, Guojordo- Alvares, Chavez- Moreno and Comacho-

Ortiz (2016: 32620) noted that the global aged population has been increasing resulting in the increase of admission of elderly patients in the ICU. Ozdermin and Dizbay (2015: 39) clarified that the need for the elderly to be admitted in the ICU is due to changes in the immunity, organ and tissue dysfunctions and underlying chronic disease in the elderly age group.

The program was adopted by an approximately half of the invited hospitals that was equipped with essential medicine list and the antimicrobial guidelines as well as the in-house laboratory. Promoting the rational use of medicine requires effective policies (Ofori-Asenso 2016:1) such as the standard treatment guidelines and essential medicine policies advocated by the World Health Organization (WHO 2002: 2). Evidence-based clinical guidelines are critical to promoting rational use of medicine (WHO 2002:3). Essential medicines have been described as those medicines that satisfy the priority health care needs of the population (WHO 2002: 3). The WHO (2002:3) suggested that the essential medicines should always be available in adequate amounts, appropriate dosage forms, with assured quality and adequate information for both the community and individual. Moreover, the essential medicine list should be based upon clinical guidelines (WHO 2002: 3). During the study period, both the clinical guidelines and essential medicine list were available.

In addition, more than 80 % of healthcare givers (ASP team members) agreed to participate in the program. The results further revealed that ASP achieved its goal of reducing the spread of antimicrobial resistance with approximately 65 % of patients in the ICU not developing HAI. Approximately 71 % of the activities for quality antimicrobial prescribing were delivered as intended.

5.5 CONCLUSION

In general, these findings indicate that the ASP has the potential for adequate to high public health impact. Furthermore, this study has demonstrated how RE-AIM evaluation model can be used to assess the impact of ASP in reducing the spread of antimicrobial resistance.

This study demonstrates that with a little support and promotion of the appropriate use of antimicrobials a significant reduction in the development of adverse

antimicrobial effects and the preventing the spread of antimicrobial resistance can be achieved.

CHAPTER 6

STRATEGIES FOR IMPROVING ASP PERFORMANCE

6.1 **INTRODUCTION**

This study examined the effectiveness of the ASP implemented in the hospital, to prescribe appropriate antimicrobials thus limiting the spread of antimicrobial-resistant bacteria. This chapter deals with the aspects of the ASP that were identified as weaknesses in the AMS program, to inform decisions on whether to expand, modify, or eliminate that particular aspect of the program. In addition, this chapter discusses the strategies suggested to optimise the performance of the AMS program.

6.2 A**NTIMICROBIAL PRESCRIBING CAPACITY**

The results of this study revealed that leadership commitment is lacking for an antimicrobial stewardship program to be successful. The leadership commitment element was found to be low (50.00 %) in capacity performance (Table 4.10). Hospital leadership support is essential to the success of ASP by ensuring the program has sufficient budget, technology, time management and resources (NQF 2016: 6; Pollack & Srinivasan 2014: 97). In this study, it was found that ASP members have other hospital duties and could not dedicate time for ASP activities. Although, ASPs are often self-sufficient through savings in both antibiotic expenditures and indirect cost, financial support enhances the success of the program (Pollack & Srinivasan 2014: 97- 98). In the studied facility no formal funding was available for running the program thus the program depended on sponsorships for sustenance.

Action plans to improve antimicrobial prescribing include convincing the hospital leadership to support the program by showing them the program's evidence of cost saving through quality care and improved patient safety due to quality antimicrobial prescribing. Communicating and regularly updating the leadership on the ASP outcome may secure leadership support and improve the program's success rate. In addition, the leadership should be convinced to ensure adequate staffing for ASP

activities in order to provide sufficient time to contribute to stewardship activities including education and training (NQF 2016: 6 - 7).

Furthermore, ASP activities should be integrated into quality improvement and/or patient safety initiatives and to ensure that the ASP team member's knowledge is regularly updated in measuring and improving antibiotic use. Leadership support should be prioritised through the accessibility and employment of qualified staff, as well as funding for information technology and policies should be availed to providers to perform their ASP duties to their best abilities (NQF 2016: 6).

6.3 CONCLUSION

Although the study showed that the performance of the ASP implemented in this facility was sufficient, there are strategies which can be used to optimise the program. This chapter demonstrated that regular evaluation of the health program is a necessity for identifying the weakness and positives so as to upscale it.

For the studied facility it was found that the ASP has no management support. There is no financial and personnel support to sustain the program and most of the healthcare workers are discouraged to participate in the program, subsequently leading to the poor performance of the program.

CHAPTER 7

RECOMMENDATIONS, LIMITATIONS, AND CONCLUSION

7.1 INTRODUCTION

This chapter discusses the recommendations, limitations of the study and suggestions for future research. The spread of antimicrobial resistance is a major public health problem that influences patients' outcome and long stay in healthcare settings. Inappropriate prescribing of antimicrobials is implicated as the critical cause of this afflicts in healthcare settings, which subsequently resulted in the birth of antimicrobial stewardship programs. The ASP's aims included the promotion of appropriate antimicrobial use with the purpose of improving patients' safety, healthcare cost and the reduction of antimicrobial resistance. Such programs are rarely evaluated to improve their performance.

This study demonstrates that the RE-AIM framework can be used to comprehensively evaluate the impact of ASP implemented in the hospital. The evaluation of reach, effectiveness, adoption, and implementation of ASP showed an adequate impact of the program on reducing antimicrobial resistance. For a comprehensive evaluation, it is recommended that all 5 RE-AIM dimensions be assessed; conversely, in this study the maintenance dimension was not included due to the short duration of the study. Therefore, a longer duration with a follow-up of more than six months is recommended.

Regarding the capacity of the hospital to prescribe quality antimicrobials, the facility leadership support was lacking. The leadership support is critical to the success of ASP and thus it is recommended that the hospital leadership should be persuaded to be more concerned about the importance of ASP.

7.2 CONTRIBUTION OF THE STUDY

Promoting appropriate use of antimicrobials in the healthcare setting will reduce unnecessary prescribing of antimicrobials and therefore, limiting the spread of antimicrobial resistance. A major contribution of this study pertains to the RE-AIM framework; to our knowledge this study is the first to assess the impact of a health

promotion program in the ICU in South Africa. Moreover, the results emphasize the beneficial effects of the program for the public health. The results of the study highlight the importance of knowing what is available or not available, with respect to the core elements of the program, to improve the success rate of the program.

7.3 LIMITATIONS OF THE STUDY

This study had several limitations:

Collection of the information of adult patients only makes the results of the study not generalizable to paediatric patients. The small number of participating hospital may not allow the generalization of the results to other hospital settings.

Microbiological data were not readily available for the study because bar-coded results were used in this facility, to report data.

The data collection period was not long enough to monitor the long-term outcome of the patients and determine the program's effectiveness. A longer study duration might have demonstrated more meaningful results by showing maintenance of the patients' improvement or re-admission to the hospital and identify the causal factors thereof. Moreover, it is difficult to measure ASP effectiveness on the reduction of resistance because such reductions may take years to be observed (Lai, Shi, Chen & Wang 2016: 80).

The participation of single public hospital for this study restricted the study from obtaining a comprehensive picture of the impact of the ASP in South African hospitals.

Another possible limitation to this study could be the sample size. Inadequate sample size has limitations that can compromise the conclusions drawn from the study and prevent the findings from being generalized (Faber and Fonseca 2014: 28; Patra 2012: 5). In order to minimize insufficient data collection, the chance of rejecting null hypothesis when it is true (Type 1 error) as well as the probability of committing type 2 error (failure to reject the hyphothesis when it is falls), **s**ome authors have recommended calculation of sample size calculation before conducting any study (Habib, Johargy Mahmood and Humma 2014:24; Patra 2012: 5). In this study the researcher calculated the sample size prior to the commencement of the

study, taking into consideration all key concepts in sample size calculation such as, the Type 1 and 2 errors, significance level, statistical power and the effect size (Habib et al. 2014:24). Sathian, Sreedharan, Baboo, Sharan, Abhilash and Rajesh (2010:4) suggest that the significant level and power must be fixed before sample determination so as to ensure the reliability of the results. For this study, the significance level was set at 5% (p = 0.05) to have a 95% confidence that the study's conclusions are accurate, and the statistical power was set at 80 %, an ideal statistical power, to recognize a likelihood of 1 in 5 of detecting a difference between groups if it exist (Habib et al. 2014: 24, 25).

Accordingly all precautions to have an appropriate sample size for this observational study were taken and an adequate sample was recruited.

7.4 RECOMMENDATIONS FOR FUTURE RESEARCH

Due to the limitations of this study, future research should consider including both public and private hospitals and broaden the scope to include different types of intensive care units and patients. It is further recommended that the study duration is increased giving allowance to follow-up studies. For a more thorough impact evaluation, the measure of cost-effectiveness (the worth of the program) is also recommended to assess if the benefits outweigh the cost of the program.

7.5 CONCLUDING REMARKS

This study intended to assess the performance of the ASP implemented in the ICU of an academic hospital, to encourage and facilitate the promotion of appropriate antimicrobial use. The implemented ASP was found to be sufficient to promote appropriate use of antimicrobials and further suggest that not only should the ASP guidelines be adhered to, but to constantly evaluate the ASP's impact on the reduction of antimicrobial use, improving patient outcomes, reducing adverse events and reducing antimicrobial resistance.

In addition, this study revealed a lack of leadership support of the ASP in the institution which raises concern about the preparedness of the institution's executives to improve the success rate and sustainability of the program. For the ASP to be successful, it requires the commitment of leadership with a guarantee of dedicated

human, financial and information technology. The lack of leadership support may contribute to the collapse of the ASP.

REFERENCES AND BIBLIOGRAPHY

Abbo, L, Smith, L, Pereyra, M, Wyckoff, M & Hooton, TM. 2012. Nurse practitioners' attitude, perceptions and knowledge about antimicrobial stewardship. *The Journal for Nurse Practitioners* **8**(5): 370-376.

Acar, JF. 1997. Consequences of bacterial resistance to antibiotics in medical practice. *Clinical Infectious Diseases* 24(1): 17-18.

Adlerberth, I, Cerquetti, M, Poilane, I, Wold, A & Collignon, A. 2000. Mechanisms of colonisation and colonisation resistance of digestive tract. Part 1; bacteria/host interactions. *Microbiol Ecology in Health and Diseases* 12(2): 223 – 239.

Adorka, M, Allen, K, Lubbe, M & Serfontein, J. 2013. The impact of healthcare providers' knowledge on appropriate prescribing of antibiotics. *J Pharm Care* 1(4): 133-140.

Adorka, M, Dikokole, M, Mitonga, K H & Allen, K. 2013. Healthcare providers' attitudes and perceptions in infection diagnosis and antibiotic prescribing in public health institutions in Lesotho: a cross sectional survey. *African Health Sciences* 13(2): 344 – 350.

Adorka, M, Mitonga, H K, Lubbe, M, Serfontein, J & Allen, K. 2014. Assessment of the appropriateness of antibiotic prescriptions in Lesotho public hospital: A novel methodology based on principles of antibiotic prescribing. *Journal of Public Health in Africa* 5: 354.

AIPC Australia Institute of Primary Care (AIPC).*2003. Measuring health promotion impacts: Aguide to impact evaluation in integrated health promotion*. Melbourne Victoria: Rural and regional health and aged care services division.

Alberta, B, Johnson, A, Lewis, J, Raff, M, Roberts, K & Walter, P. 2002. *Molecular Biology of the Cell.* 4th Edition. New York: Garland Science.

Albiger, B, Dahlberg, S, Henriques-Normark, B & Normark, S. 2007. Role of the innate immune system in host defence against bacterial infections: focus on the Toll-like receptors. *Journal of Internal Medicine* 261: 511 – 528.

Al-Durgham, L M &. Barghash, M A 2015. Factor and cluster analysis as a tool for patient segmentation applied to hospital marketing in Jordan. *American J Operat Res*, 2015, 5, 293-306

Alison H Holmes, Luke S P Moore, Arnfi nn Sundsfj ord, Martin Steinbakk, Sadie Regmi, Abhilasha Karkey, Philippe J Guerin, Laura J V Piddock. 2015. Antimicrobials: access and sustainable effectiveness 2. Understanding the mechanisms and drivers of antimicrobial resistance. Lancet. Retrieved from: http:dx.doi.org/10.1016/SO140-6736(15)00473-0 (Accessed on: 2019/01/06)

Alumrana, A, Houa, X-Y & Hurst, C. 2012. Validity and reliability of instruments designed to measure factors influencing the overuse of antibiotics. *Journal of Infection and Public Health* 5: 221- 232.

Amoakoh-Coleman, M, Kayode, GA, Brown-Davies, C, Agyepong, IA, Grobbee, DE, Klipstein-Grobusch, K & Ansah, EK. 2015. Completeness and accuracy of data transfer of routine maternal health services data in the greater Accra region, *BMC Research Notes* 1-9.

Anyanwu, IE & Williams, FI. 2015. *Improving validity of tests through improved test development procedures.* Quality assurance Department. Nigeria: National Examinations Council (NECO).

Baba, CT, Oliviera, IM, Silva, AEF, Vieira, LM, Cerri, NC, Florindo, AA & Gomes, GA. 2017. Evaluating the impact of a walking program in a disadvantaged area: using the RE-AIM framework by mixed methods. *BMC Public Health* 17(1): 709 -718.

Babamahmoodi, F, Ahangarkani, F & Davoudi, A. 2015. Hospital-acquired infections, bacterial causative agents and antibiotic resistance pattern in intensive care units at teaching hospitals in North of Iran. *Int J Med Invest* 4: 152-160.

Baggot, JD. 1998. Antimicrobial selection, administration and dosage**.** *J S.Afr.Vet.Ass.* 69(4): 174–185.

Baker, S, Thomson, N, Weill, F X & Holt, K E. 2017. Genomic insight into the emergence and spread of antimicrobial-resistant bacterial pathogens. *Science* 360: 733 – 738.

Baktygul, K, Marat, B, Ashirali, Z, Harun-or-Rashid, MD & Sakamoto, J. 2011. An assessment of antibiotics prescribed at the secondary health-care level in the Kyrgyz Republic. *Nagoya J. Med. Sci* 73 :157 -168.

Bamford, C, Brink, A, Govender, N, Lewis, D A, Perovic, O, Botha, M, Harris, B, Keddy, KH, Gelband, H & Duse, A G. 2011. The global resistance partnership: Part V. Surveillance activities. *South Afr Med J* 101: 579 – 582.

Baquero, F & Garau, J. 2010. Prudent use of antimicrobial agents: revisiting concepts and estimating perspectives in a global world. *Enferm Infect Microbiol Clin* 28(8): 497 – 488.

Barbosa, TM & Levy, SB. 2000. The impact of antibiotic use on resistance development and persistence. *Drug Resistance Updates* 3: 303 – 311.

Bird, DK. 2009. The use of questionnaires for acquiring information on public perception of natural hazards and risk mitigation – a review of current knowledge and practice. *Nat Hazards Earth Syst Sci* 9:1307- 1325.

Bolarinwa, OA. 2015. Principles and methods of validity and reliability testing of questionnaires used in social and health science researches. *Niger Postgrad Med J*. 22:195-201.

Boonsong, S, Chongtrakool, P, Srisangkaew, S, & Santanirand, P. 2011. Prevalence and distribution of most common ICU pathogens in a Thai-university hospital during a 5-year period. *BMC Proc* 5 (6): 244.

Borg, MA. 2009. Addressing the challenge of antibiotic resistance in Maltese healthcare settings. *Malta Medical Journal* 21(02): 8 - 12

Boucher, HW, Talbot, GH, Bradley, JS, Edwards, JE, Gilbert, D, Rice, LB, Scheld, M, Spellberg, B & Bartlett, J. 2009. Bad bugs, no drugs: no ESKAPE! an update from the Infectious Diseases Society of America. *Clin. Infect. Dis.* 48: 1–12.

Boyles, T H, Whitelaw, A, Bamford, C, Moodley, M, Bonorchis, K, Morris, V, Rawoot, N, Naicker, V, Lusakiewicz, I, Black, J, Stead, D, Lesosky, M, Raubenheimer, P, Dlamini, S & Mendelson, M. 2013. Antibiotic stewardship ward rounds and a dedicated prescription chart reduce antibiotic consumption and pharmacy costs without affecting inpatient mortality or re-admission rates. *PLOS ONE* 8(12): 1-7.

BrckaLorenz, A, Chiang, Y & Nelson Laird, T. 2013. Internal consistency. FSSE Psychometric portfolio, Retrieved from: www.fsse.indiana.edu. (Accessed on: 18 October 2017).

Brink, A. Feldman, C, Duse, A, Gopalan, D, Grolman, D, Mer, M, Naiker, S, Paget, G, Perovik, O & Richards, G. 2006.Guideline for the management of nosocomial infections in South Africa. *South Afr Med J* 21(4): 152 – 160.

Brink, AJ, Messina, AP, Feldman, C, Richards, GA, Becker, PJ, Goff, DA, Bauer, KA Nathwani, D & van den Bergh, D. 2016. Antimicrobial stewardship across 47 South African hospital: an implementation study. *Lancet Infect Dis* 16:1017 – 1025.

Brinkac, L, Voorhies, A, Gonzalez, A & Nelson, EK. 2017. The threat of antimicrobial resistance on human microbe *Microb Ecol* 74(4): 1001 – 1008.

Bulmer, M. 2008. *The ethics of social research*. Chapter 4. In: Gilbert Nigel (ed). Researching social life. 3rd Edition. London: Sage.

Burns, SN & Grove, SK. 2003. *Understanding nursing research: building an evidence=based practice*. 3rd Edition. Philadelphia: Saunders.

Byarugaba, DK. 2010. *Mechanisms of antimicrobial resistance*, In: de J Sosa, A, Byarugaba, D, Amabile-Cuevas, CF, Hsueh, P-R, Kariuki, S & Okeke, In. Eds.

Antimicrobial resistance in developing countries. New York: Springer Science-Business Media.

Cadena, J, Taboada, CA, Burgess, DS, Ma, JZ, Lewis II, JS, Freytes, CO & Patterson JE. 2007. Antibiotic cycling to decrease bacterial antibiotic resistance: a 5-year experience on a bone marrow transplant unit. *Bone Marrow Transplant* 40 (2): 151 – 155.

Carlson, MD & Morrison, RS. 2009. Study design, precision, and validity in observational studies. *Journal of Palliative Medicine* 12(1): 77 – 82.

Catholic Relief Services (CRS). 2011. *Holistic organizational capacity assessment instrument (HOCAI): Guide*, Chapter 2: Baltimore, USA. Retrieved from: www.crsprogramquality.org. (Accessed on: 13 December 2017).

CDC see Centers for Disease Control and Prevention.

CDC. 2013. Antibiotic resistant threats in the United States. Retrieved from: www.cd.gov/drugresistance/pdf/ar-threat-2013-508.pdf (Accessed 15 April 2017).

CDC. 2014. *Core Elements of Hospital Antibiotic Stewardship Programs.* Atlanta, GA: US Department of Health and Human Services, CDC. Retrieved from: www.cdc.gov/getsmart/healthcare/implementation/core-elements.html. (Accessed 8 July 2016).

Cecchetto, FH & Pellanda, LC. 2014. Construction and validation of a questionnaire on the knowledge of healthy habits and risk factors for cardiovascular disease in schoolchildren. *J Pediatr (Rio J)*. 90:415-419.

Cha, R, Michienzi, SM & Hsaiky, L. 2012. Antimicrobial pharmacokinetics and pharmacodynamics in the treatment of nosocomial gram-negative infections. *Adv Pharmacoepidem Drug Safety* 1: 5.

Chang, Y- Y, Chen, H-P, Lin, C-W, Tang, J- J, Hsu, T- Y, Weng, Y- C, Lee, Y- M, Wang, W-S & Lo, S-S. 2017. Implementation and outcomes of an antimicrobial

stewardship program: effectiveness of education. *Journal of Chinese Medical Association* 80:253 – 359.

Charani, E, Castro-Sanchez, E, Sevdalis, N, Kyratsis, Y, Drumright, L, Shah, N & Holmes, A. 2013. Understanding the determinants of antimicrobial prescribing within hospitals: the role of "prescribing etiquette". *Clinical Infectious Diseases* 57(2): 188 – 186.

Chaves, NJ, Cheng, AC, Runnegar, N, Kirschner, J, Lee, T & Buising, K. 2014. Analysis of knowledge and attitude surveys to identify barriers and enablers of appropriate antimicrobial prescribing in three Australian tertiary hospitals. *Internal Medicine Journal* 44(6): 568-574.

Chiang, C-Y, Uzoma, I, Moore, RT, Gilbert, M, Duplantier, A J & Panchal, RG. 2018. Mitigating the Impact of Antibacterial Drug Resistance through Host-Directed Therapies: Current Progress, Outlook, and Challenges. *mBio* 9 (1): e01932- 37.

Chiwaridzo, M, Chikasha, TN, Naidoo, N, Dambi, JM, Tadyanemhandu, C, Munambah, N & Chizanga, PT. 2017. Content validity and test-retest reliability of a low back pain questionnaire in Zimbabwean adolescents. *Archives of Physiotherapy* 7: 3 – 14.

Christensen, LB, Johnson, BR & Turner LA. 2015. *Research methods, design, and analysis*.12th Edition. Boston: Pearson.

Chung, GW, Wu JE, Yeo CL, Chan D & Hsu LY. 2013. Antimicrobial stewardship: a review of prospective audit and feedback systems and an objective evaluation of outcomes. *Virulence* 4(2): 151 -157.

Compernolle, S, De Cocker, K, Lakerveld, J, Mackenbach, JD, Nijpels, G, Oppert, J-M, Rutter, H, Teixeira, PJ, Cardon, G & De Bourdeaudhuij, I. 2014. A RE-AIM evaluation of evidence-based multilevel interventions to improve obesity-related behaviours in adults: a systematic review (the SPOTLIGHT project). *International Journal of Behavioral Nutrition and Physical Activity* 11:147.

Cook, DA & Beckman, TJ. 2006. Current concepts in validity and reliability for physcometric instruments: theory and application. *American Journal of Medicine* 119(2): 166.e7 – 166.e16.

Cosgrove, SE & Carmeli, Y. 2003. The impact of antimicrobial resistance on health and economic outcomes. *Clin Infect Dis* 36:1433–1437.

Crowther-Gibson, P, Govender, N, Lewis, DA, Bamford, C, Brink, A, von Gottenberg, A, Klugman, K, du Plessis, M, Fali, A, Harris, B, Keddy, KH & Botha, M. 2011. PART IV GARP: Human infections and antibiotic resistance. *South Afr Med J (SAMJ*) 101(8):567 -578.

Davey, P, Brown, E, Charani, E, Fenelon, L, Gould, IM, Holmes, A, Ramsay, CR, Wiffen, PJ & Wilcox, M. 2013. *Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev* Issue 4. The Cochrane Collaboration. John Wiley & Sons, Ltd.

Dawson, C, 2002. *Practical research method: A user-friendly guide to mastering research*. United Kingdom: How to books. Retrieved from www.howtobooks.co.uk (Accessed on: 9 February 2017).

De Angelis, G, Restuccia, G, Cauda, R & Tacconelli, E. 2011. How could we reduce antibiotic use in critically ill patients? *Infect Disord Drug Targets* 11:376-383.

Dellinger, EP, Gross, PA, Barrett, TL, Krause, PJ, Martone, WJ, McGowan, JE, Jr., Sweet, RL, & Wenzel, RP. 1994. Quality standard for antimicrobial prophylaxis in surgical procedures. *CID* 18: 422 – 427.

Dellit, TH, Owens, RC, McGowan, JE, Jr, Gerding, DN, Weinstein, RA, Burke JP, Huskins, WC, Paterson, DL, Fishman, NO, Carpenter, CF, Brennan, PJ, Billeter M & Hooton, TM. 2007. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis*. 44:159 – 177.

de With, K, Allerberger, F, Amann, S, Apfalter, P, Brodt, H-R , Eckmanns, T, Fellhauer M, Geiss, HK, Janata, O, Krause, R, Lemmen, S, Meyer, E, Mittermayer, H, Porsche, U, Presterl, E, Reuter, S, Sinha, B, Straub, R, Wechsler-Fordos, A, Wenisch, C & Kern, WV. 2016. Strategies to enhance rational use of antibiotics in hospital: a guideline by the German Society for Infectious Diseases. *Infection* 44:395–439.

Dhillon, H K, Zaini, Z A, Quek, K F, Singh, H J, Kaur, G & Rusli, B N. 2014. Exploratory and confirmatory factor analyses for testing validity and reliability of the Malay language questionnaire for urinary incontinence diagnosis (QUID). *Open Journal of Preventive Medicine* 4: 844-851.

Dik, J-W, Poelman, R, Friedrich, AW, Panday, PN, Lo- Ten- Foe, JR, van Gemert-Pijnen, JEWC, Niestens, HGM, Hendrix, R & Sinha, B. 2015. An integrated stewardship model: antimicrobial, infection prevention and diagnostic (AID). *Future Microbiology* 11(1): 93 – 102.

Dimitrov, D M & Rumrill, P D, Jr. 2003. Pretest-posttest designs and measurement of change. *Work* 20: 159–165.

Doron, S & Davidson, L E. 2011. Antimicrobial stewardship**.** *Mayo Clin Proc* 86 (11):1113-1123.

Dunton, GF, Lagloire, R & Robertson, T. 2009. Using the RE-AIM framework to evaluate the statewide dissemination of a school-based physical activity and nutrition curriculum: ‘‘exercise your options’’. *American Journal of Health Promotion* 23 (4): 229- 232.

Duse, A. 2005. Infection control in developing countries with particular emphasis to South Africa. *SAJEI* 20:37-41.

Duse, AG. 2011. Editorial. The Global Antibiotic Resistance Partnership (GARP). Part 2. Global Antibiotic Resistance Partnership -Situation Analysis. Antibiotic use and resistance in South Africa. *S Afr Med J* 101 (8): 551.

Dzidic, S, Suskovic, J & Kos, B. 2008. Antibiotic resistance mechanisms in bacteria: biochemical and genetic aspects. *Food Technol Biotechnol* 46(1): 11 – 21.

Edwards, R, Drumright, LN, Kiernan, M. & Holmes, A. 2011. Covering more territory to fight resistance: considering nurses' role in antimicrobial stewardship. *Journal of Infection Prevention* 12: 6-10.

Elliott, A C, Hynan, L S, Reisch, J S & Smith, JP. 2006. Preparing data for analysis using Microsoft Excel. *J. Invest Med*, 54(6): 334 – 341.

Essack, SY. 2006. Review: strategies for the prevention and containment of antibiotic resistance. *SA Fam Pract* 48(1): 51.

European Centre for Disease Prevention and Control (ECDC) 2011. *Annual epidemiological port 2013: reporting on 2011 surveillance data and 2012 epidemic intelligence data*. Stockholm: ECDC.

European Commission (EC). 2010. *European textbook on ethics in research.* Belgium: Luxembourg publications office of the European Commission.

Euse AM, Zoccali C, Jager KJ & Dekker FW. 2009. Cohort studies: Prospective versus retrospective. *Nephron Clin Pract* 113: 214–217.

Faber, J & Fonseca, L M. 2014. How sample size influences research outcomes. *Dental Press J Orthod* 19(4): 27 – 29.

Farris, RP, Will, JC, Khavjou, O & Finkelstein, EA. 2007. Beyond Effectiveness: evaluating the public health impact of the WISEWOMAN Program. *American Journal of Public Health* 97(4): 641- 647.

Field, AP. 2000. *Discovering statistics using SPSS for Windows: advanced technique for the beginner*. London: Sage..

Filice, G, Drekonja, D, Greer, N, Butler, M, Wagner, B, MacDonald, R, Carlyle, M, Rutks, I, Wilt, T. 2013. Antimicrobial stewardship programs in inpatient settings: A systematic review. *Infection Control and Hospital Epidemiology* 35(10):1209-1228.

Fong, DYT. 2001. Data management and quality assurance. *Drug Information Journal*, 35: 839 – 844.

GARP-India working group, 2011. Rationalizing antibiotic use to limit antibiotic resistance. *Indian J Med Res* 134: 281- 294.

Gauteng Department of health. 2016. *Annual report 2015/ 2016*. Retrieved from: www.gauteng.gov.za/government/departments/Annual%20Report/GDH%20aNNUAL%20Report%202015-2016.pdf. (Accessed on 13 May 2017).

Garrouste-Orgeas,M, Timsit, JF, Tafflet, M, Misset,B, Zahar,JR, Soufir, l, Lazard, T, Jamali, S, Mourvillier, B, Cohen, Y, De Lassence, A, Azoulay, E, Cheval, C, Descorps-Declere, A, Adrie, C, de Beauregard M-A C & Carlet, J. 2006. Excess risk of death from intensive care unit- acquired nosocomial bloodstream infections: a reappraisal. *Clinical Infectious Diseases* 42(8): 1118-1126.

Gelband H & Duse, AG. 2001. Global Antibiotic Resiatance Partnership, Part 2. Situation analysis: antibiotic use and resistance in South Africa. *SAMJ* 101(8): 549-596.

Gertler P J, Martinez S, Premand P, Rawlings L B & Vermeersch C M J. 2016. *Impact evaluation in practice*, 2nd Edition. Washington DC: World Bank.

Giaquinto-Cilliers, MGC, Hoosen, MZ, Govender, T & Van der Merwe, LW. 2014. Bacteriological profile at Kimberley hospital burns unit: a four-year retrospective study. *Wound Healing Southern Africa* 7(1):29-32.

Glasgow RE, McKay, HG, Piette, JD & Reynolds, KD. 2001. The RE-AIM framework for evaluating interventions: what can it tell us about approaches to chronic illness management? *Patient Educ Couns* 44(2): 119 – 127.

Glasgow, RE, Klesges, LM, Dzewaltowski, DA, Estabrooks, PA &. Vogt, TM.2006. Evaluating the impact of health promotion programs: using the RE-AIM framework to form summary measures for decision making involving complex issues. *Health Education Research* 21 (5): 688 – 694.

Glasgow, RE, Vogt, TM & Boles, SM. 1999. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. *Am J Public Health* 89:1322–1327.

Gould, IM. 2011. *The antibiotic paradox.* In: IM. Gould and JWM van der Meer (eds.). Antibiotic policies: controlling hospital acquired infection. New York: Springer Science + Business Media.

Group of Enteric, Respiratory and Meningeal disease Surveillance in South Africa(GERMS-SA). 2007. *GERMS-SA Annual report, 2006*. National Institute for Communicable Diseases, a branch of the National Health Laboratory Services, Johannesburg, South Africa. Retrieved from: http://www.nicd.ac.za/units/germs/germs.htm. (Accessed on 24 October 2016).

Guerri-Fernandez, R, Villar-Garcia, J, Herriera-Fernandez, S, Trenchs-Rodriguez, M, Fernandez-Morato, J, Maro, L, Sancho, J, Grande, L, Clara, A, Grau, S & Horrcaidda, J P. 2016. An antimicrobial stewardship program reduces antimicrobial therapy duration and hospital stay in surgical wards. *Rev Esp Quimioter* 29(3): 119-122.

Gyssens, I C, Van Den Broek, P J, Ullberg, B-J K, Hekster, Y A & Van Der Meer, J W M.1992. Optimizing antimicrobial therapy: A method for antimicrobial drug use evaluation**.** *Antimicrob Chemother* 30: 724- 727.

Habib, A, Johargy, A, Mahmood, K& Humma 2014. Design and determination of the sample size in medical research. *IOSR-JDMS* 13(5): 21 – 31.

Hackshaw,A. 2008. Small studies: strength and limitations. *Eu Resp J* 32: 1141 – 1143.

Harris, AD, Bradham, DD, Baumgarten, M, Zuckerman, IH, Fink, JC & Perencevich EN. 2004. The use and interpretation of quasi-experimental studies in infectious diseases. *Clinical Infectious Diseases* 38:1586–1591.

Harris, AD, McGregor, JC, Perencevich, EN, Furuno,JP, Zhu, J, Peterson, DE & Finkelstein, J. 2006. Thu use and interpretation of quasi-expermental studies in

medical informatics. *Journal of the American Medical Informatics Association* 13(1): 16- 23.

Hawkey, PM. 1998. The origins and molecular basis of antibiotic resistance. *BMJ* 317 (7159): 657 – 660.

Ho, AD, & Yu, CC. 2014. Descriptive Statistics for modern test score distributions: Skewness, kurtosis, discreteness and ceiling effects. *Educational and Psychological Measurement* 75(3): 365–388.

Horan, TC, Andrus, M, Dudeck, MA. 2008. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 36: 309-332.

Howard, P, Pulcini, C, Hara, G L, West, R M, Gould, I M, Harbarth, S & Nathwani, D. 2015. An international cross-sectional survey of antimicrobial stewardship programmes in hospitals. *J Antimicrob Chemother* 70: 1245–1255.

Huye, HF, Connell, CL, Crook, LB, Yadrick, K & Zoellner, J. 2014 Using the RE-AIM framework in formative evaluation and program planning for a nutrition intervention in the lower Mississippi Delta. *J Nutr Educ Behav* 46:34-42.

Impact Evaluation Working group. 2012. Impact evaluation: a discussion paper for AustAID practitioners. AusAID Office of Development Effectiveness: Australia. Retrieved from: www.dfat.gov.au/aid/how-we-measure-performance/ode/document/impact-evaluation-discussion-paper.pdf. (Accessed on: 21 March 2017).

Jauregui, E, Pacheco, AM, Soltero, EG, O'Connor, TM, Castro, CM, Estabrooks, P A, McNeill, LH & Lee, RE. 2015. Using the RE-AIM framework to evaluate physical activity public health programs in Mexico. *BMC Public Health* 15:162 – 170.

Jeong, H-J, Jo, H-S, Oh, M-K & Oh, H-W. 2015. Applying the RE-AIM framework to evaluate the dissemination and implementation of clinical practice guidelines for sexually transmitted infections. *J Korean Med Sci* 30: 847-852.

Johnson, I & Banks, V. 2017. Antibiotic stewardship in critical care. *BJA Education* 17(4): 111 – 116.

Joung, MK, Lee, J-A, Moon, S-Y, Cheong, HS, Joo, E-J, Ha, Y-E, Sohn, KM, Chung, SM, Suh, GY, Chung, DR, Song, J-H & Peck, KR. 2011. Impact of de-escalation therapy on clinical outcomes for intensive care unit-acquired pneumonia. *Critical Care* 15: 79.

Kaki, R, Elligsen, M, Walker, S, Simor, A, Palmay, L & Daneman, N. 2011. Impact of antimicrobial stewardship in critical care: A systematic review. *J Antimicrob Chemother* 66(6): 1223 – 1230.

Kamangar, F. 2012. Confounding variables in epidemiology studies: basic and beyond. *Archive of Iranian Medicine* 15(8): 508 – 516.

Kanada, N, Chen, GT, Inohara, N & Nunez, G. 2013. Control of pathogens and pathobionts by the gut microbiota.Nat Immunol 14(7): 685 – 690.

Kapil, A. 2005. The challenge of antibiotic resistance:need to contemplate. *Indian J Med Res* 121: 83 – 91.

Khan, HA, Baig, FK, Mehboob, R. 2017. Nosocomial infections: epidemiology, prevention, control and surveillance. *Asian Pac J Trop Biomed* 7(5): 478 – 482.

Kim, H-Y. 2013. Statistical notes for clinical researchers: assessing normal distribution (2) using skewness and kurtosis. *Restorative Dentistry and Endodontics* 38(1): 52 – 54.

Kimberlin, CL & Winterstein, AG. 2008. Validity and reliability of measurement instruments used in research. *Am J Health-Syst Pharm* 65: 2276- 2284.

King, DK, Glasgow, RE & Leeman-Castillo, B. 2010. Re-aiming RE-AIM: using the model to plan, implement, and evaluate the effects of environmental change approaches to enhancing population health. *Am J Public Health* 100:2076–2084.

Kollef, MH & Micek, ST. 2012. Antimicrobial stewardship program: mandatory for all ICUs. *Critical Care* 16(6): 179 – 180.

Kollef, MH, Sherman, G, Ward, S & Fraser, VJ. 1999. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. *Chest* 115 (2):462-474.

Kolman, S, Geertsema, H, van den Berg, D & Goff, D. 2016. Engaging pharmacy personnel in antimicrobial stewardship using a novel method of teaching. *S Afr Pharm J* 83(1): 25-29.

Kothari, CR. 2004. *Research methodology: Methods and techniques*. 2nd Revised Edition, New Dehli: New Age International.

Krzowska-Firych, J, Kozłowska, A, Sukhadia, T & Al-Mosawi, L K . 2014. Hospital-acquired infections caused by antibiotic resistant bacteria. *Postepy Nauk Medycznych* XXVII (11): 783 – 786.

Kumar, S & Varela, MF. 2013. *Molecular mechanisms of bacterial resistance to antimicrobial agents.* In: Mendez-Vilas, A Eds. Microbial pathogens and strategies for combating them: science, technology and education. Spain: Formatex Research Center: Badajoz.

Lai, C-C, Shi, Z-Y, Chen, Y-H & Wang, FD. 2016. Effects of various antimicrobial stewardship programs on antimicrobial usage and resistance among common gram-negative bacilli causing health care-associated infections: a multicenter comparison. *Journal of Microbiology, Immunology and Infection* 49:74- 82.

Lakshmi, R, Nusrin, KS, Ann, GS & Sreelakshmi, KS. 2014.The role of beta-lactamases in antibiotic resistance : a review. *Int Res J Pharm* 5(2):37- 40.

Laxminarayan, R, Duse, A, Wattal, CH, Zaidi, AKM, Wertheim, HFL, Sumpradit, N, Vlieghe, E, Levy, Hara, G, Gould, IM, Goossens, H, Greko, C, So, AD, Bigdeli, M, Tomson, G, Woodhouse, W, Ombaka, E, Peralta, A Q, Qamar, FN, Mir, F, Kariuki, S,

Bhutta, ZA, Coates, A, Gergstrom, R, Wright, GD, Brown, ED & Cars, O. 2013. Antibiotic resistance – the need for global solutions. *Lancet* 13: 1057-1098.

Laximinarayan, R, Matsoso, P, Pont, S, Brower, C, Rettingen, J-A, Klugman, K & Davies, S. 2016. Antimicrobials: access and sustainable effectiveness1. Access to effective antimicrobials: a world challange. *Lancet* 387: 168 – 175.

Lehohla, P. 2013. *Use of health facilities and levels of selected health conditions in South Africa: findings from the general house-hold survey*. Pretoria: Statistics South Africa.

Leuthner, KD & Doern, GV. 2013. Antimicrobial stewardship program. *Journal of Clinical Microbiology* 51(12): 3916 – 3920.

Levy, SB. 2001. Antibiotic resistance: consequences of inaction. *Clinical Infectious Diseases*, 33(S 3):S124–9.

Lim, C, Takahashi, E, Hongsuwan, M, Wuthiekanun, V, Thamlikitkul, V, Hinjoy, S, Day, NPJ, Peacock, SJ, Limmathurotsakul, D. 2016. Epidemiology and burden of multidrug-resistant bacterial infection in a developing country. *eLife*, 5:e18082.

Lisboa, T & Nagel, F. 2011. Infection with multi-resistant agents in the ICU: how to escape. *Rev Bras Ter Intensiva* 23(2): 120 – 124.

Livorsi, D, Comer, AR, Matthias, MS, Perencevich, EN & Bair, MJ. 2015. Factors influencing antibiotic-prescribing decisions among inpatient physicians: a qualitative investigation. *Infect Control Hosp Epidemiol* 36 (9): 1065–1072.

Liwa, AC & Jaka H. 2015. *Antimicrobial resistance: Mechanisms of action of antimicrobial agents.* In: A. Méndez-Vilas, Ed. The battle against microbial pathogens: basic science, technological advances and educational programs. Spain: Formatex Research Centre.

Llor C & Bjerrum L. 2014. Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem**.** *Ther Adv Drug S Afr* 5(6): 229– 241.

Lundine, KM, Nelson, S, Buckley, R Putnis, S & Duffy, PJ. 2010. Adherence to perioperative antibiotic prophylaxis among orthopaedic trauma patients. *Can J Surg* 53(6): 367 – 372.

Luyt, C-E, Brechot, N, Trouillet, J-L & Chastre, J. 2014. Antibiotic stewardship in the intensive care unit. *Critical Care* 18:480.

MacDougall, C & Polk, RE. 2005. Antimicrobial stewardship programs in healthcare systems. *Clin Microbiol Rev* 18: 638–56.

Mansor, M, Haque, M, Sheikh, S A, Choon, L C & Zin, A M 2016.Reliability and factor analysis of general health questionnaire in Malay version among women with abnormal pap smear results. AMJ 9(9): 357–364.

Martin,SJ, Micek, ST & Wood, GC. 2010. Antimicrobial resistance: consideration as an adverse drug event. *Crit Care Med*. 38(6):155-161.

Mathers, N, Fox, N & Hunn, A. 2007. Surveys and Questionnaires. Yorkshire & the Humber: The NIHR RDS for the East Midlands.

Mbim, NE, Mboto, CI & Agbo, BE. 2016. A Review of Nosocomial Infections in Sub-Saharan Africa. *British Microbiology Research Journal* 15(1): 1-11.

McDowell, I. 2006. *Measuring health: a guide to rating scales and questionnaire*. 3rd edition. Oxford: Oxford University Press.

McGann, P, Snesrud, E, Maybank, R, Corey, B, Ong, AC, Clifford, R, Hinkle, M, Whitman, T, Lesho, E & Schraecher, KE. 2016. *Escherichia coli* harbouring *mcr-1* and bla_{CTX-M} on a novel IncF Plasmid: First report of *mcr-1* in the United States. *Antimicrob Agents Chemother* 60 (7): 4420 – 4421.

McKibben, L, Horan, T, Tokars, J I, Fowler, G, Cardo, D M, Pearson, M L, Brennan, P J, & the Healthcare Infection Control Practices Advisory Committee 2005. Guidance on public reporting of healthcare-associated infections: recommendations

of the Healthcare Infection Control Practices Advisory Committee. *Am J Infect Control* 33(4): 217 – 226.

Mendelson, M, Rettingen, J-A, Gopinathan, U, Hamer, DH, Wertheim, H, Basiyat, B, Buttler, C, Tomson, G & Balasejaram, M. 2016. Antimicrobials: access and sustainable effectiveness 3. Maximising access to achieve appropriate human antimicrobial use in low-income and middle-income countries. *Lancet* 387: 188 – 198.

Mendelson, M & Matsoso, MP. 2015. Guest Editorial. The South African Antimicrobial Resistance Strategy Framework. *South African Medical Journal*, 105(5): 54.

Mendelson, M Whitelaw, A, Nicol, M & Brink, A. 2012. Wake up, South Africa! The antibiotic 'horse' has bolted. *South African Medical Journal* 102(7): 607 – 608.

Messina, AP, van den Bergh, D & Goff, DA. 2015. Antimicrobial stewardship with pharmacist intervention improves timeliness of antimicrobials across thirty-three hospitals in South Africa. *Infect Dis Ther* 4 (1): 5–14.

Michael, CA, Dominey-Howes, D & Labbate, M. 2014.The antimicrobial resistance crisis: causes, consequences, and management. *Frontiers in Public Health* 2(145): 1- 8.

Mihaly, V, Orsolya, B, Monica, O, Anna, P A, Hajna, K, Maria, C S & Judit, K. 2016. The incidence and risk factors of nosocomial infections in ICU, *Acta Medica Marisiensis* 62(3):304-308.

Ministry of health Malaysia (MOHM). 2014. Protocol on antimicrobial stewardship program in health-care facilities, Retrieved from: www.moh.govt.maylaysia. (Accessed on: 23 April 2016).

Mishra, PH, Panarjee, P & Gosain, H. 2014. Study of healthcare associated infections (HAI*). Merit Research Journal of Biochemistry and Bioinformatics* 2(2): 38 – 48.

Mokkink, LB, Terwee, CB, Patrick, DL, Alonso, J, Stratford, PW, Knol, DL, Bouter, XM & de Wet, HCW. 2012. COSMIN checklist manual. *BMC Research Methodology*10:22 – 29.

Morency-Potvin, P, Schwartz, DN & Weinstein, RA. 2017. Antimicrobial stewardship: how the microbiology laboratory can right the ship. *Clin Microbiol Rev* 30:381– 407.

Morrow, B. 2015. Ethical considerations for critical care research. *S Afr J Crit Care* 31(2): 34 – 35.

Moussaoui, RE, Opmeer, BC, Bossuyt, PM, Speelman, P, de Borgie CAJM & Prins, JM. 2004. Development and validation of a short questionnaire in community acquired pneumonia. *Thorax* 51: 591 – 595.

National Collaborating Centre for Methods and Tools (NCCMT). 2010. *Assessing the public health impact of health promotion initiatives*: RE-AIM evaluation framework Hamilton, ON: McMaster University. Retrieved from www.nccmt.ca/knowledge-repositories/search/70 (Accessed on: 11 October 2017).

NDoH see National Department of Health

NDoH. 2015. Antimicrobial resistance national strategy framework 2014 – 2024. Retrieved from: www.nda.agric.za/docs/media/A5%20Antimicrobial%20Resistance%20National%20Strategy%20Framework%202014-2024_final.pdf. (Accessed on 7 December 2016).

NDoH. 2017. Guidelines on implementation of the antimicrobial strategy in South Africa: one health approach and governance. Retrieved from: www.nahf.co.za/wp-content/uploads/Antimicrobial-Stewardship-Guidelines-Governance_June2017.pdf (Accessed on: 12 October 2017).

NDoH. 2015. *Ethics in health research; principles and structures* 2nd Edition.Pretoria: Department of health. Retrieved from: www0.sun.ac.za/research/assets/files/intergrity_and_Ethics/DoH%202015%20Ethics

%20in%20Health%20Research%20-%20Principles,%20Processes%20and%20Structures%202nd%20Ed.pdf. (Accessed on 13 May 2017).

Newland, JG, Stach, ML, De Lurgo, SA, Hedican, E, Yu, D, Herigon, JC, Prasad, PA, Jackson, MA, Myers, AL & Zaoutis, TE. 2012. Impact of a prospective –audit- with –feedback antimicrobial stewardship program at a children's hospital. *Journal of the Pediatric Infectious Diseases Society* 1(3): 179 – 186.

NQF see National quality forum.

National Quality Forum 2016. *National quality partners' playbook: Antibiotic stewardship acute care*. Washington DC: National Quality Forum.

Nilholm, H, Holmstrand, L, Ahl,J, Mansson, F, Odenholt,I, Tham, J, Melander E & Resman, F. 2015. Profoundly reduced antibiotic use without negatively affecting patient outcomes. *Open Forum Infectious Diseases* 2(2): 1- 10.

Njoku, JC & Hermsen, ED. 2010. Antimicrobial stewardship in the intensive care unit: A focus on potential pitfalls. *Journal of Pharmacy Practice* 23(1): 50-56.

Norris, A, Jackson, A & Khoshnood, K. 2012. Exploring the ethics of observational research: the case of an HIV study in Tanzania. *AJOB Prim Res* 3(4): 30–39.

Nyasula, P, Murray, J, Perovic, O, & Koornhof H. 2012. Antimicrobial resistance surveillance among nosocomial pathogens in South Africa: a systematic review of published literature. *J Exp Clin Med* 4(1): 8-13.

Ofori-Asenso R& Agyeman AA. 2016. Irrational use of medicines: a summary of key concepts. *Pharmacy* 4 (35): 1.

Owonikoko, TK. 2013. Upholding the principles of autonomy, beneficence, and justice in phase I clinical trials. *The Oncologist* 18: 242 –244.

Om, C, Daily, F, Vlieghe, E, McLaughlin, J C & McLaw, M-L. 2006. If it's a broad spectrum, it can shoot better: inappropriate antibiotic prescribing in Cambodia. *Antimicrobial Resistance and Infection Control* 5:58.

Omulo, S, Thumbi, SM, Njenga, MK & Call, DR. 2015. A review of 40 years of enteric antimicrobial resistance research in Eastern Africa: What can be done better? *Antimicrobial resistance & Infection Control* 4: 1-13.

Organisation for Economic Co-operation and Development – Development Assistance Committee (OEDC-DAC). 2002. 'Evaluation of development programmes, DAC Criteria for Evaluating Development Assistance', Retrieved from: www.oecd.org/dac/evaluation/daccriteriaforevaluatingdevelopmentassistance.htm. (Accessed on: 21 March 2017).

Ory, MG, Altpeter, M, Belza, B, Helduser, J, Zhang, C, & Smith, ML. 2015. Perceptions about community applications of re-aim in the promotion of evidence-based programs for older adults. *Evaluation and the Health Professions* 38(1): 15-20.

Oxford, J, Goossens, H, Schedler, M, Sefton, A, Sessa, A & van der Velden, A. 2013. Factors influencing inappropriate antibiotic prescription in Europe. *Education for Primary Care* 24: 291–293.

Ozdermir, K & Dizbay, M. 2015. Nosocomial infection and risk factors in elderly patients in intensive care units. *Journal of Microbiology and Infectious Disease* 5(1): 38 – 43.

Ozer, B, Tatman-Otkun, M, Memis, D & Otkun, M. 2010. Nosocomial infections and risk factors in intensive care unit of a university hospital in Turkey. *Cent. Eur. J. Med* 5(2): 203-208.

Paruk, F, Richards, G, Scribante, J, Bhagwanjee, S, Mer, M & Perrie, H. 2012. Antibiotic prescription practices and their relationship to outcome in South African intensive care unit; findings of the prevalence of infection in South African intensive care units (PISA) study. *South African Medical Journal* 102(2): 613 – 616.

Patra, P. 2012. Sample size in clinical research, the number we need. *Int J Med Sc Publ Health*, 1(1): 5 – 9.

Pedrosa, RBS, Rodrigues, RCM, Padilha, KM, Gallani, MCBJ, Alexandre, NMC. 2016. Factor analysis of an instrument to measure the impact of disease on daily life. *Rev Bras Enferm* 69(4): 650-657.

Peersman, G. 2014. *Overview: Data collection and analysis methods in impact evaluation. Methodological Briefs: Impact Evaluation 10.* Florence: UNICEF Office of Research.

Pennings, JME & Smidts, A. 2000. Assessing construct validity of risk attitude. *Management Science* 46(10): 1337- 1348.

Perron, GG, Inglis, RF, Pennings, PS & Cobey, S. 2015. Fighting microbial drug resistance: A primer on the role of evolutionary biology in public health. *Evolutionary Applications* 211 – 222.

PHE see Public Health England

PHE. 2015. *Start smart - then focus: antimicrobial stewardship toolkit for English hospitals*. ESPAUR SSTF, Retrieved from: https://www.gov.uk/government/publications/english-start smart-then focus-espaur-report (Accessed on: 15 August 2016).

Pillai, J, Yazicioglu, C, Moeng, S, Rangaka, T, Monareng, T, Jayakrishnan, R, Veller, M, & Pinkus, D. 2015. Prevalence and patterns of infection in critically ill trauma patients admitted to the trauma ICU, South Africa. *J Infect Dev Ctries* 9 (7):736-742.

Pinder, RJ, Sallis, D, Berry, A & Chadborn, T. 2015.*Antibiotic prescribing and behaviour change in healthcare setting: literature review and behavioural analysis*. London-UK: Department of Health and Public Health England.

Pinto, RO, Pattussi, M P, do Prado Fontoura, L, Poletto, S, GrapigliaI, V L, Balbinot, A D, Teixeira, V A & Horta, R L. 2016. Validation of an instrument to evaluate health promotion at schools. *Rev Saúde Pública* 50:2- 12.

Planta, M B. 2007. The role of poverty in antimicrobial resistance. *J Am Board Fam Med* 20:533–539.

Polit, D & Hungler, B, 1999. *Nursing research: principles and methods*. 6th edition. Philadelphia: Lippincott Company.

Polit, DF & Beck, CT. 2010. *Essentials of nursing research: appraising evidence for nursing research*. 7th edition. Philadelphia: Lippincot Williams and Wilkins Publishers.

Polit, DF & Beck, TC. 2004. *Nursing research : Principles and methods*, 7th Edition. Philadelphia; London: Lippincott Williams and Wilkins.

Pollack, L A & Srinivasan, A. 2014. Core elements of hospital antibiotic stewardship programs from the centers for disease control and prevention. *Clinical Infectious Diseases* 59 (3):S97–100.

Pourhoseingholi, MA, Vahedi, M & Rahimzadeh, M. 2013. Sample size calculation in medical studies. *Gastroenterol Hepatol Bed Bench* 6(1): 14-17.

Premanandh, J, Samara, BS & Mazen, AN. 2015. Race against antimicrobial resistance requires coordinated action: an overview. *Frontiers in Microbiology* 6: 1 – 6.

Pulcini, C & Gyssens, I C. 2013. How to educate prescribers in antimicrobial stewardship practices. *Virulence* 4(2):192–202.

Reichenheim, M E, Hokerberg, Y H M & Maraes, C L. 2014. Assessing construct structural validity of epidemiological measurement tools: a seven-step roadmap. *Methodological Issues* 30(5):927-939.

Ribet, D & Cossart, P. 2015. How bacterial pathogens colonize their host and invade deeper tissues. *Micobes and Infection* 17: 173 – 183.

Rogers, P. 2014. *Overview of impact evaluation*, *methodological briefs: Impact evaluation 1*. Florence: UNICEF Office of Research.

SAASP working group, 2012. 1st South African antibiotic stewardship program (SAASP). Working group meeting. 12TH February 2012, Radisson Blu Hotel, Sandton, Gauteng.

Sande-Bruinsma, N, Grundmann, H, Verloo, D, Tiemersma, E, Monen, J, Goossens, H, Ferech, M. 2008. Antimicrobial drug use and resistance in Europe. *Emerg Infect Dis* 14:1722–30.

Saga, T & Yamaguchi, K. 2009. History of antimicrobial agents and resistant bacteria. *JMAJ* 52(2): 103–108.

Santajit, S & Indrawattana, H. 2016. Mechanism of antimicrobial resistance in ESKAPE pathogens. *Biomed Research International* 1 - 9.

Schellack, N, Pretorius, R & Messina, A P. 2016. *Esprit de corps*': Towards collaborative integration of pharmacists and nurses into antimicrobial stewardship programmes in South Africa. *South African Medical Journal* 106(10): 973-974.

Schoenbach, VJ.1999. Understanding the fundamentals of epidemiology: an evolving text. Retrieved from www.epidemiolog.net. (Accessed on: 7 August 2016)

Schreiber, JB, Stage, FK, King, J, Nora, A & Barlow, EA. 2006. Reporting structural equation modelling and confirmatory factor analysis results: a review. *The Journal of Education Research* 99 (6): 323 – 337.

Shao, L-W, Ni, L-M, Gao, C-H, Wei, J-H, Zhong, Z- F, Meng, S-Q, Yang, W-B & Liu, J-H. 2016. The incidence and risk factors of nosocomial infections in intensive

care unit in China: an epidemiological study of 1718 patients. *Int J Clin Exp Med* 9(12): 23642-23649.

Shlaes, DM, Gerding, DN, John, JF, Craig, WA, Bornstein, DL, Duncan, RA, Eckman, MR, Farrer, WE, Greene, WH, Lorain, V, Levy, S, McGowan, JE, Paul, SM, Ruskin, J, Tenover, FC & Watanakunakorn, C. 1997. Society for Healthcare Epidemiology of America and Infectious Diseases Society of America joint committee on the prevention of antimicrobial resistance in hospitals. *Infect Control Hosp Epidemiol* 18:275 – 291.

Sinatra, I, Carubia, L, Marchese, V, Aprea, L, D'Alessandro, N, Mammina, C & Torregrossa, MV. 2013. Prevalence survey of healthcare-associated infections and antimicrobial use at the university hospital "Paolo Giaccone", Palermo, Italy. *J Prev Med Hyg* 54: 200-204.

Singh, H, Arora, E, Thangaraju, P, Singh, J & Natt, NK. 2013. Antimicrobial resistance: new patterns, emerging concepts and prevention. *J Rational Pharmacother Res* 1(2): 95 – 99.

Siniscalco, M T & Auriat, N. 2005. Questionnaire design, In, (Ed.) Ross K N., Module 8, Quantitative research method in education planning, International Institute for Educational Planning/UNESCO. Retrieved from: www.unesco.org/iiep. (Accessed on 25 September 2016).

Skodvin, B, Aase, K, Charani, E, Holmes, A & Smith, I. 2016. An antimicrobial stewardship program initiative: A qualitative study on prescribing practices among hospital doctors. *Antimicrobial Resistance and Infection Control* 4:24- 32.

Solis-Vernandez, PS, Vidales- Reyes, M, Gorza-Gonzalez, E, Guojardo- Alvarez, G, Chavez- Moreno, S & Camacho-Ortiz, A. 2016. Hospital-acquired infections in elderly versus younger patients in an acute care hospital. *Int J Infect* 3(1): e32620.

Soto, GJ, Martin, GS & Gong, MN. 2013. Healthcare disparities in critical illness. *Crit Care Med* 41(12): e3182.

Song, J-H. 2003. Introduction: the goals of antimicrobial therapy. *Int J Infect Dis* 7: 1-4.

Spellberg, B, Powers, JH, Brass, EP, Miller, LG & Edwards, JE Jr. 2004**.** Trends in antimicrobial drug development: implications for the future. *Clin. Infect. Dis* 38: 1279–1286.

Stones, DH & Krachler, A-M. 2015. Fatal attraction: how bacterial adhesions affect host signalling and what we can learn from them. *Int J Mo. Sci* 16:2626 – 2640.

Summer, J. 2009. *Principles of healthcare ethics.* Chapter2. In: Morris Eileene (ed). Health care ethics: critical issues for the 21st country, 2nd . Edition. Sudbury:Jones and Bartlett.

Suresh, KP & Chandrashekara, S. 2012. Sample size estimation and power analysis for clinical research studies. *Journal of Human Reproductive Science* 5: 7-13.

Swe Swe-Han, K & Coovadia, Y. 2010. Prevalence of antimicrobial resistant bacteria from adult ICUs and the Burns unit at a large tertiary hospital in Durban. *Int J Infect Control* 1-8.

Sweet, A, Ginis, KAM, Estabrooks, PA & Latimer-Cheung A E. 2014. Operationalizing the RE-AIM framework to evaluate the impact of multi-sector partnerships*. Implementation Science* 9: 74 – 84.

Tacconelli, E. 2009. Antimicrobial use: risk driver of multidrug resistant microorganisms in healthcare settings. *Curr Opin Infect Dis* 22(4): 352 – 358.

Tadesse, B T, Ashley, EA, Ongarello, S, Havumaki, J, Wjegoonewardens, M, Gonzalez, I J & Dittrich, S, 2017. Antimicrobial resistance in Africa: a systematic review. *BMC Infect Dis* 17: 616 – 633.

Tavakol, M, & Dennick, R. 2011. Making Sense of Cronbach's Alpha. *International Journal of Medical Education*, 2: 53-55.

Thanasegaran, G. 2009. Reliability and validity issues in research*. Integration and Dissemination Research Bulletin* 4: 35 -40.

Theise, M S. 2014. Observational and interventional study design type: An overview. *Biochemia Medica* 24: 199- 210.

Toma, A & Deyno, S. 2015. Overview on mechanisms of antibacterial resistance. *International Journal of Research in Pharmacy and Biosciences* 2 (1): 27-36.

Truter, I. 2015. Antimicrobial prescribing in South Africa using a large pharmacy database. *South Afr J Infect Dis* 30(2): 52-56.

Valles, J, Leon, C & Alvarez-Lerna, F. 1997. Nosocomial bacteremia in critically ill patients: a multi center study evaluating epidemiology and prognosis. *Clin Infect Dis* 24: 387-395.

van de Sande-Bruinsma, N, Grundmann, H, Verloo, D, Tiemersma,E, Monen, J, Goossens, H, Ferech, M & the European Antimicrobial Resistance Surveillance System and European Surveillance of Antimicrobial Consumption Project Groups. 2008. Antimicrobial drug use and resistance in Europe. *Emerging Infectious Diseases* 14 (11): 1727 – 1730.

van den Bergh D.2009. Antibiotic stewardship: Q and A. *Best Care Always!* 1.

van Hoek, AHAM, Mevius, D, Guerra, B, Mullany, P, Roberts, AP & Aarts, AJM. 2011. Acquired antibiotic resistance genes: an overview. *Frontiers in Microbiology* 2(203): 1- 27.

Varley, AJ, Sule, J & Absolom, AR. 2009. Principles of antibiotic therapy. *Continuing Education in Anaesthesia, Critical Care & Pain* 9 (6): 184 – 188.

Victorian Government Department of Human Services. 2008. *Measuring health promotion impacts: A guide to impact evaluation in integrated health promotion.* Melbourne: Stream Solution.

Vincent, J-L, Bassetti, M, Francois, B, Karam, G, Chastre, J, Torres, A, Roberts, JA, Taccone, FS, Rello, J, Calandra, T, De Backer, D, Welte & Antonelli, M. 2016. Advances in antibiotic therapy in the critically ill. *Critical Care* 20:133.

Vincent, J-L, Rello, J, Marshall, J, Silva, J, Anzueto, E, Martin, C D, Moreno, R, Lipman J, Gomersall, C, Sakr, Y & Reinhart, K. 2009. International study of prevalence and outcomes of infection in the intensive care units. *JAMA* 302(21): 2323 – 2329.

Vitrat, V, Hautefeuille, S, Janssen, C, Bougon, D, Sirodot, M & Pagani, L. 2014. Optimizing antimicrobial therapy incritically ill patients. *Infection and Drug Resistance* 7: 261–271.

Wasserman, S, Boyles, T & Mendelson, M. 2014. A pocket guide to antibiotic prescribing for adults in South Africa. SAASP. Retrieved from:www.fidssa.co.za/content/document/SAASP_antibiotic_guidelines_2015.pdf. (Accessed on: 20 November 2017).

Watkins, MW. 2018. Exploratory factor analysis: a guide to best practice. *Journal of Black Psychology* 44(3): 219– 246.

Weinstein, RA. 1998. Nosocomial infection: Update. *Emerg Infect Dis* 4: 416-420.

Wetzel, A. 2011. *Factor analysis methods and validity evidence: A systematic review of instrument development across the continuum of medical education*. Thesis.

WHO see World Health Organization

WHO. 2001. *Health research methodology: a guide for training in research methods.* Second Edition, Geneva: World Health Organization

WHO. 2002. *Promoting rational use of medicines: core components*. WHO Policy perspectives on medicines. No: 5. Geneva: World Health Organization.

WHO. 2002. *Prevention of hospital-acquired infections: a practical guide*. 2nd Edition. Malta: World Health Organization.

WHO. 2012. *The evolving threat of antimicrobial resistance: options for action*. Geneva: World Health Organization.

WHO. 2013. *Ethical issues in patient safety research: interpreting existing guidance*. Geneva: World Health Organization.

WHO. 2016*. International statistical classification of diseases and related health problems.* 10th revision, 5th Edition, volume 1, WHO publications, Geneva: World Health Organization.

WHO. 2017. *Antibacterial agents in clinical development: an analysis of antibacterial clinical development pipeline, including tuberculosis*. Geneva: World Health Organization.

Willemsen,I, der Kooij, T, van Benthem,B. Wille,J & Kluytmans, J. 2010. Appropriateness of antimicrobial therapy: a multicentre prevalence survey in the Netherlands, 2008–2009. *Euro Surveill* 15 (46): 1- 7.

Williams, B; Brown, T & Onsman, A. 2010. Exploratory factor analysis: A five-step guide for novices. *Journal of Emergency Primary Health Care* 8 (3): 1 – 13.

Woolhouse, M, Waugh, C, Perry MR & Nair H. 2016.Global disease burden due to antibiotic resistance- state of evidence. *Journal of Global Health* 6(1): 1 -5.

Yesilbag, Z, Karadeniz, A, Basaran, S & Kaya, FO. 2015. Nosocomial infection and risk factors in intensive care unit of a university hospital. *Journal of Clinical Experimental investigation* 6(3): 233 – 239.

Zilahi, G, Artigas, A, & Martin-Loeches, I. 2016. What's new in multidrug-resistant pathogens in the ICU? *Ann. Intensive Care* 6:96.

Zulkepli, M, Sipan, I & Jibril, J D.2014. An exploratory factor analysis and reliability analysis for green affordable housing criteria instrument**.** *International Journal of Real Estate Studies,* 11 (4): 9 - 21 ,

ANNEXURES

ANNEXURE A: ETHICS APPROVAL FROM THE UNIVERSITY

UNISA university of south africa

RESEARCH ETHICS COMMITTEE: DEPARTMENT OF HEALTH STUDIES
REC-012714-039 (NHERC)

1 February 2017

HSHDC/605/2017
Mr BE Nkosi
Student: 5373-902-7

Supervisor: Dr S Sibanda
Qualification: PhD
Joint Supervisor: Prof MM Moleki

Dear Mr BE Nkosi

Decision: Ethics Approval

Name: Mr BE Nkosi

Proposal: Evaluation of impact of antimicrobial stewardship in limiting the spread of antimicrobial resistance in Gauteng Province.

Qualification: DDPCHS04

Thank you for the application for research ethics approval from the Research Ethics Committee: Department of Health Studies, for the above mentioned research. Final approval is granted for the duration of the research period as indicated in your application.

The application was reviewed in compliance with the Unisa Policy on Research Ethics by the Research Ethics Committee: Department of Health Studies on 1 February 2017.

The proposed research may now commence with the proviso that:

1) *The researcher/s will ensure that the research project adheres to the values and principles expressed in the UNISA Policy on Research Ethics.*

2) *Any adverse circumstance arising in the undertaking of the research project that is relevant to the ethicality of the study, as well as changes in the methodology, should be communicated in writing to the Research Ethics Review Committee, Department of Health Studies. An amended application could be requested if there are substantial changes from the existing proposal, especially if those changes affect any of the study-related risks for the research participants.*

University of South Africa
Preller Street, Muckleneuk Ridge, City of Tshwane
PO Box 392 UNISA 0003 South Africa
Telephone: +27 12 429 3111 Facsimile: +27 12 429 4150
www.unisa.ac.za

3) *The researcher will ensure that the research project adheres to any applicable national legislation, professional codes of conduct, institutional guidelines and scientific standards relevant to the specific field of study.*

4) *[Stipulate any reporting requirements if applicable].*

Note:
The reference numbers [top middle and right corner of this communiqué] should be clearly indicated on all forms of communication [e.g. Webmail, E-mail messages, letters] with the intended research participants, as well as with the Research Ethics Committee: Department of Health Studies.

Kind regards,

Prof L Roets
CHAIRPERSON
roetsl@unisa.ac.za

Prof MM Moleki
ACADEMIC CHAIRPERSON
molekmm@unisa.ac.za

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ANNEXURE B: LETTER REQUESTING PERMISSION TO DO RESEARCH

377 Nkuna Street
Zone 5 Meadowlands
Gauteng
Soweto
1852

Chris Hani Baragwaneth Hospital
PO Bertsham
Chris Hani
2013
South Africa

Dear Dr R Mathivha

RE: Request for permission to conduct a study in your institution

I am writing to request a permission to conduct a study in your hospital. The research I proposed is part of the requirements for the D Litt et Phil study with the University of South Africa. My supervisor is Dr S Sibanda. The title of my study is: The impact of stewardship of antimicrobial use in limiting the spread of antimicrobial resistance in South Africa. The purpose of this project is to assess the effectiveness of the implemented antimicrobial stewardship programs and identify their deficiencies, to act on them and improve on the program's impact.

Identifying the deficiencies of the antimicrobial stewardship program implemented in South African hospitals, will aid in optimising the promotion of appropriate use of antibiotics subsequently preventing and controlling unnecessary prescribing and misuse of antibiotics. The study will contribute substantially to strengthening infection control practices, as well as, reducing hospital acquired infections. Critically ill

patients 18 years and above, admitted in the intensive care unit and developed signs and symptoms of bacterial infection after 48 - 72 hours of admission.

Data will be collected using structured and standardized Questionnaires. The daily routine will not be disturbed, and patients will not be interfered with. I will keep all the data I collect completely confidential, and I will not use any patient's names in any research reports. Any information that I present will not be linked to any personal information that could be used to identify individual students. I am confident that I have taken the necessary steps to ensure that my research will be conducted in ways that meet ethical standards.

Attached to this letter is the copy of my proposal, research ethics approval letter, data collection forms and consent forms. Should you require any further information, please do not hesitate to contact me (E-mail: 53739027@mylife.unisa.ac.za, Cell number: 0731097498) or my supervisor (E-mail : sibans1@unisa.ac.za, Tel: +27 12 429 6003).

Yours Faithful

Mr B E Nkosi
Cell number: 0731097498
Email: 53739027@mylife.unisa.ac.za

ANNEXURE C: APPROVAL LETTER MEDICAL ADVISORY COMMITTEE

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 30th June 2017

TITLE OF PROJECT:

Evaluation of impact of antimicrobial stewardship in limiting the spread of antimicrobial resistance in Gauteng Province

UNIVERSITY: UNISA

Principal Investigator: B N NKOSI

Department: Biomedical /ICU

Supervisor : S Sibanda

Permission Head Department (where research conducted): Yes

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO / management of Chris Hani Baragwanath Academic Hospital is accordingly informed and the study is subject to:-

- **Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.**
- The Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- The MAC will be informed of any serious adverse events as soon as they occur
- Permission is granted for the duration of the Ethics Committee Approval.

Recommended
(On behalf of the MAC)
Date: 30/06/2017

Approved/Not Approved
Hospital Management
Date: 03/07/17

ANNEXURE D: APPROVAL LETTER FROM CHBAH'S ICU

health and
social development
Department: Health and Social Development
GAUTENG PROVINCE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL
Intensive Care unit

Dr JM Brown
Jacqui.Brown@wits.ac.za
Tel: 0119381596
Fax:0119381595

9th June 2017

To whom it may concern

Re: Permission to collect patient data in Chris Hani Baragwanath Hospital Intensive Care unit

Title of research project: Evaluation of impact of antimicrobial stewardship in limiting the spread of antimicrobial resistance in Gauteng Province

Investigator: Mr BE Nkosi

Permission is hereby granted for Mr BE Nkosi to collect patient data in ICU for the purpose of his study. The data collected will be used for his PhD.. Permission is subject to ethics approval.

Regards

Dr JM Brown
Deputy Head: Intensive Care Unit
Chris Hani Baragwanath Hospital
Soweto
Affiliated to University of the Witwatersrand

ANNEXURE E: LETTER FOR REQUEST THE PARTICIPATION OF ASP TEAM MEMBERS IN THE STUDY

377 Nkuna Street

Zone 5 Meadowlands

1852

Chris Hani Baragwanath Academic Hospital

Department of ICU

03- 09- 2017

Dear Sir/ Madam

RE: Participation in antimicrobial stewardship assessment study.

My name is Bongani Nkosi and I am currently registered with UNISA for a PhD. I am doing research on the effectiveness of microbial stewardship programmes that aims to reduce inappropriate use of antimicrobials, while improving patients' outcome and preventing the spread of antimicrobial resistance. Attached is an antimicrobial stewardship programme questionnaire.

You were approached because your participation in this study will assist in determining the effectiveness of antimicrobial stewardship programme in promoting the prudent use of antimicrobials in hospitals. The questionnaire intends to collect information on the capacity of the hospital to prescribe antimicrobials. Information on the availability of financial, personnel and structural support for prescribing quality antimicrobials will be collected. Furthermore, this study is for the fulfilment of the requirements for the doctoral degree in the subject Health Studies at UNISA.

Hope my request will receive favourable response

Yours Sincerely

Bongani Nkosi

E- mail : 53739027@mylife.unisa.com

Cell: 073 109 7498

ANNEXURE F: CONSENT FORM FOR REVIEWING PATIENTS' MEDICAL RECORDS.

INFORMED CONSENT FORM FOR REVIEWING PATIENTS' MEDICAL RECORDS AND USE IN A RESEARCH STUDY

PROJECT TITLE

Impact of antimicrobial stewardship in limiting the spread of antimicrobial resistance in South Africa

Principal Investigator: Mr Bongani Nkosi

Contact: Cell number: 0731097498; email: 53739027@mylife.unisa.ac.za

Supervisor: Dr Sibanda; (012) 4296003; email: sibans1@unisa.ac.za

What you should know about this research study:

- We give you this consent so that you may read about the purpose, risks, and benefits of this research study.
- The main goal of research studies is to gain knowledge that may help future patients.
- We cannot promise that this research will benefit you.
- You have the right to refuse to take part or agree to take part now and change your mind later.
- Whatever you decide, it will not affect your regular care.
- Please review this consent form carefully. Ask any questions before you decide.
- Your participation is voluntary.

PURPOSE

This study aims to comprehensively assess the effectiveness of antimicrobial stewardship program in promoting the judicious prescribing and use of antimicrobials in South African hospitals, to identify its deficiencies. Subsequently, the effect of the program on limiting the spread of antimicrobial resistant bacteria will be measured.

PROCEDURES AND DURATION

Information about the appropriateness of antimicrobial prescribing will be collected using a structured questionnaire and reviewing of patients' medical record. The process of data collection will consist of 2 phases: A baseline phase will entail the extraction of information from medical records of patients who have developed signs and symptoms of infection within 48h of admission to the ICU. There will be no interference with daily routine practice. The information collected will include: patients' demographics and clinical information. Additionally, a questionnaire on the capacity of the hospital to prescribe judicious antimicrobials will be completed. The second phase will take place after 4 days of the empirical antibiotic therapy, and it will involve the extraction of microbiological test results, review of the empirical antimicrobial therapy and patients' outcome, without disturbing the daily routine practice.

RISKS AND DISCOMFORTS

This is a non-intrusive study and there will be no interference with the daily routine practice of the hospital. There is no foreseeable risk of harm or discomfort to participants.

CONFIDENTIALITY

To secure the confidentiality of the participants, data from individual participant will be collected and anonymised by aggregating the individual information according to specific characteristic. Therefore, participant's identification will be concealed.

ADDITIONAL COSTS

No additional costs will be incurred by your participation.

VOLUNTARY PARTICIPATION

Participation in this study is voluntary therefore you are free to choose either to participate or not to participate. If you decide not to participate in this study, your decision will not affect your future relations with the hospital, its personnel, and associated hospitals. At any given time, you are free to withdraw your consent and to discontinue participation at any time without penalty.

OFFER TO ANSWER QUESTIONS

Before you sign this form, please ask any questions on any aspect of this study that is unclear to you. You may take as much time as necessary to think it over.

AUTHORIZATION

You are deciding whether to participate or not to participate in this study. Your signature indicates that you have read and understood the information provided above, have had all your questions answered, and have decided to participate.

Research Title: Impact of antimicrobial stewardship in limiting the spread of antimicrobial resistance in South Africa

_____ _____

Name and signature of Research Participant Date

_____ _____

Signature of Researcher Date

YOU WILL BE GIVEN A COPY OF THIS CONSENT FORM TO KEEP

If you have any questions concerning this study or consent form beyond those answered by the investigator, including questions about the research, your rights as a research participant or research-related injuries; or if you feel that you have been treated unfairly and would like to talk to someone other than a member of the research team, please feel free to contact the UNISA Higher Degrees Ethics Committee.

ANNEXURE G: FINAL QUESTIONNAIRE FOR DATA EXTRATION

ANTIMICROBIAL STEWARDSHIP IMPACT ASSESSMENT QUESTIONNAIRE

Introduction

Antimicrobial stewardship programmes aim to reduce inappropriate use of antimicrobials, while improving patients' outcome and preventing the spread of antimicrobial resistance.

PHASE 1

APPROPRIATENESS OF ANTIMICROBIAL PRESCRIBING

Name of Facility**:**_____ Name of data collector:_____

Ward: _____ Date of data collection:_____

_____

Patient's code:_____

DERMOGRAPHICAL DATA

1. **How old is the patient?** Specify the age_____
2. **Gender (*Check X only one box)***

Female ☐ Male ☐

3. **Ethnic origin *(Check X only one box)***

Black ☐ White ☐ Indian ☐ Coloured ☐ Other (Specify) ☐

4. **Highest qualification *(Check X only one box)***

Primary ☐ High School ☐ FET/College ☐ University ☐

5. **Marital status *(Check X only one box)***

Single ☐ Married ☐ Divorced ☐ Widowed ☐

HEALTH RELATED INFORMATION

6. **Does the patient suffer from any chronic disease? *(Check X only one box)***

   No ☐ Yes ☐

   If yes, please specify_____

7. **What was the initial diagnosis upon admission?** _____

   _

8. **Does the patient require mechanical ventilation? *(Check X only one box)***

   No ☐ Yes ☐

9. **What is the clinical indication for the initial prescription of antibiotics**?

   Medical prophylaxis ☐ Surgical prophylaxis ☐ Therapeutic ☐

10. **Is a combination of antimicrobials prescribed to the patient during ICU stay?**

    No ☐ Yes ☐

    Specify the following:

    Number of antimicrobials_____

    Name_____

    Dosage_____

    Mode of administration_____

Spectrum _____

11. Is the microbiological specimen obtained? *(Check X only one box)*

No ☐ Yes ☐

If yes, please tick the relevant source

Sputum ☐ Urine ☐ Swabs ☐ Blood ☐ Fluids ☐

Other ☐

PHASE 2

REVIEW OF THE ANTIMICROBIAL THERAPY

12. What are the results of microbiological test? (*Check X only one box)*

Positive ☐ Negative ☐

If yes specify the bacteria_____

13. Is the microbe susceptible to the antimicrobial treatment? *(Check X only one box)*

No ☐ Yes ☐

14. Is the prescribed antimicrobial treatment reviewed? *(Check X only one box)*

No ☐ Yes ☐

If yes check X the relevant

Therapy stopped ☐

The route changed ☐

Dosage altered ☐

The spectrum altered ☐

15. **How long has the patient been on prescribed antimicrobial treatment?**

    Specify number of days_____

16. **Are there any hospital acquires events observed?** ***(Check X only one box)***

    No ☐ Yes ☐

    (If yes specify) _____

17. **What is the patient's outcome?** ***(Check X only one box)***

    Still hospitalised ☐ Discharged ☐ Died ☐

18. **How long is the patient's stay in the ICU?**

    Specify in days_____

Thank you for participating

PHASE 3

ANTIMICROBIAL PRESCRIBING CAPACITY

Phase 3, is to be completed by the member of the ASP team or the Head nurse. It intends to collect information on the availability of financial, personnel and structural support as well as prescribing guidelines for quality antimicrobials.

Name of the Facility_____Name of data collector:_____

_____

Data collection date:_____HOD/ Team member_____

1. **Which of the following personnel are involved in improving the quality of antimicrobial prescribing in your facility?** ***(Check X all that is relevant)***

   Infection prevention and protection ☐

   Microbiology laboratory ☐

   Clinicians ☐

   Nurses ☐

   Other please specify_____

2. **How often does your ASP team meet?** ***(Check X only one box)***

   Never ☐ Seldom ☐ Frequent ☐

3. **Does your facility provide IT support to facilitate day to day monitoring prescription, antimicrobial use and data reporting?** ***(Check X only one box)***

   Yes☐ No ☐

4. **Which antimicrobial stewardship strategy is used in your facility for promoting the improvement of the quality of antimicrobials prescribed? *(Check X only one box)***

   Prospective audit with direct intervention and feedback ☐

   Formulary restriction and preauthorisation requirement ☐

   Other be specify_____

5. **Who is responsible for programme outcome of stewardship activities in your facility? *(Check X only one box)***

   Physician ☐ Pharmacist ☐ Physician and pharmacists ☐

6. **How does your facility financially support the antimicrobial stewardship activities? *(Check X only one box)***

   Own funding ☐ Sponsor ☐

7. **Does your facility provide education to clinicians and any other relevant personnel on improving the quality of antimicrobial prescribing? *(Check X only one box)***

   Yes ☐ No ☐

8. **Does your facility have an essential medicine list authorized for acquisition of medicines by hospital? *(Check X only one box)***

   Yes ☐ No ☐

9. **Is a set of essential antimicrobials always available in your facility? *(Check X only one box)***

   Yes ☐ No ☐

10. **Is the essential medicine list in your institution regularly revised? (Check X only one box)**

    Yes ☐ No ☐

11. **Does your facility have evidence-based local antimicrobial guidelines for the diagnosis and treatment of common infections?** ***(Check X only one box)***

Yes ☐ No ☐

12. **How often does your facility audit antimicrobial guidelines?** ***(Check X only one box)***

Never ☐ Seldom ☐ Frequent ☐

13. **Is the prescribing behaviour within your facility audited?** ***(Check X only one box)***

Yes ☐ No ☐

14. **Does your facility identify and address non-compliance to local antimicrobial prescribing guidelines?** ***(Check X only one box)***

Yes ☐ No ☐

15. **Is regular feedback provided to prescribing physician?** ***(Check X only one box)***

Yes ☐ No ☐

16. **Does your facility provide regular surveillance and reporting of inappropriate prescribing and resistance patterns?** ***(Check X only one box)***

Yes ☐ No ☐

17. **Does your facility track and report antibiotic use?** ***(Check X only one box)***

Yes ☐ No ☐

If yes, how is antibiotic use monitored? ***(Check X only one box)***

By number of days of therapy (DOT)? ☐

By number of grams of antibiotics used (Defined Daily Dose: DDD)? ☐

By direct expenditure for antibiotics over time (purchasing costs)? ☐

Other specify_____

18. **Does your facility have an in-house microbiology laboratory?** ***(Check X only one box)***

Yes ☐ No ☐

19. **Does the in-house laboratory routinely perform antimicrobial susceptibility tests?** ***(Check X only one box)***

Yes ☐ No ☐

20. **Is an antibiogram regularly distributed in your facility?** ***(Check X only one box)***

Yes ☐ No ☐

21. **Does your facility track rates of *Clostridium difficile?* *(Check X only one box)***

Yes ☐ No ☐

22. **Has the quality of antimicrobial prescribing improved since the implementation of the antimicrobial stewardship program?** ***(Check X only one box)***

Yes ☐ No ☐

23. **Does your facility have a follow-up system to enhance long-term improvements?** ***(Check X only one box)***

Yes ☐ No ☐

Thank you for participating

ANNEXURE H: DATA DICTIONARY FOR THE DESCRIPTION OF STUDY VARIABLES FOR ANALYSIS

Variable name	Role	Label	Units	Type	Values Codes/range
Identification	Predictor	Patient's ID	Numerical	Continuous	1-62
Age	Confounder	Age at admission date	Years	Continuous	19 – 38 = 1 39 – 58 = 2 59 – 78 = 3 79 – 98 = 4
Sex	Confounder	Gender of the patients	Text	Categorical	Male= 1 Female= 2
Race	Confounder	Classification of patients according to racial groups.	Text	Categorical	Black = 1 White = 2 Coloured = 3 Indian = 4
Marital status	Confounder	Marital status of the participants	Text	Categorical	Single = 1 Married = 2 Divorced = 3 Widowed = 4
Level of education	Confounder	The highest level of education acquired	Text	Categorical	None = 0 High school = 1 College/FET = 2 University = 3
Chronic diseases	Confounder	The presence or absence of chronic diseases	Numerical	Binary	Yes = 1 No = 0
Ventilation	Confounder	The presence or absence of mechanical ventilation.	Numerical	Binary	Yes = 1 No = 0
Diagnosis groupings	Predictor	Diagnosis grouping upon admission	Text	Classification of the illness	Infectious disease Genitourinary system

					Digestive system. Respiratory system. Circulatory system. Endocrine and nutrition Injury, poisoning =7
Initial diagnosis	Predictor	Initial diagnosis upon admission	Text	Diagnosed illness	Illness
Secondary diagnosis	Predictor	Compounding diagnosis	Text	Secondary illness	Illness
Severity of illness index	Predictor	The severity of the illness	Numerical	Discrete	Minor = 1 Moderate = 2 Major = 3 Catastrophic = 4
Clinical indicator	Predictor	Clinical indications for antimicrobial prescribing.	Numerical	Binary	Surgical prophylaxis= 1 Medical prophylaxis = 2 Therapeutic = 3
Combination antimicrobials	Predictor	Is a combination of antimicrobials prescribed to the patient?	Numerical	Binary	Yes =1 No = 0
Antimicrobials	Predictor	The type of prescribed antimicrobials	Text	Antimicrobials	Antimicrobial type
Antimicrobial spectrum	Predictor	The range of the empirical prescribed antimicrobials.	Numerical	Binary	Narrow =1 Broad = 2
Microbiological test	Outcome	Test for Microbial growth and their susceptibility to antimicrobials	Numerical	Binary	Yes = 1 No = 0
Microbiological results	Outcome	Microbiological test results	Numerical	Binary	Positive = 2 Negative = 1 Not tested = 0
Microbes	Outcome	The identified growing microbe	Numerical	Discrete	Not tested = 0 No growth= 1 Bacterial name= 2
Susceptibility results	Outcome	The effectiveness of antimicrobial treatment	Numerical	Discrete	Not tested = 0 Resistant = 1 Sensitive = 2
Treatment	Predictor	The number of treatment	Numerical	Discrete	1-4

		prescribed			
Adminitration	Predictor	The mode of administering antimicrobials	Numerical	Binary	IV = 1 Oral =0
Dosage	Predictor	The dosage prescribed for the indication	Numerical	Discrete	500 mg - 2g
Length of treatment	Predictor	Length of treatment	Numerical	Continuous	1 – 3 days = 1 4 – 6 days = 2 7 - 9 days = 3
Treatment review	Predictor	Altering of the treatment	numerical	Discrete	Stopped = 0 Changed = 1 Not tempered with = 2
Healthcare acquired events	Outcome	ICU acquired events	Numerical	Binary	Yes = 1 No = 0
Length of stay	Outcome	Length of stay in the ICU	Numeric	Categorical	4 – 7 days= 1 8 – 11 days = 2 12 –15 days = 3 16 – 19 days = 4
Patient outcome	Outcome	Status of the patient	Numerical	Discrete	Discharged= 0 Still admitted = 1 Dead = 2

ANNEXURE I: CHECKLIST FOR THE CORE ELEMENTS OF THE HOSPITAL ANTIBIOTIC STEWARDSHIP PROGRAM.

Key element	Questions	No	Yes
Leadership support	Does your facility have a formal, written statement of support from leadership that supports antibiotic stewardship?		
	Does your facility receive any budgeted financial support for antibiotic stewardship activities?		
Accountability	Is there a physician leader responsible for program outcomes of antibiotic stewardship activities at your facility?		
Drug expertise	Is there a pharmacist leader responsible for working to improve antibiotic use at your facility?		
	Does any of the staff below work with the stewardship leaders to improve antibiotic use?		
	Clinicians		
	Infection prevention and epidemiology		
	Quality assurance		
	Microbiology (Laboratory)		
	Information technology		
	Nursing		
Actions to support optimal antibiotic use			
Policies	Does your facility have a policy that requires prescribers to document in the medical record during order entry, a dose, duration and indication for all antibiotic prescriptions?		
	Does your facility have facility-treatment recommendation, based on national guidelines and susceptibility, to assist with antibiotic selection for common clinical conditions?		
Specific interventions	Are the following actions to improve antibiotic prescribing conducted in your facility?		
Broad intervention	Is there a formal procedure for all clinicians to review the appropriateness of all antibiotics 48 h after the initial orders?		
	Do specific antibiotic agents need to be approved by a physician or pharmacist prior to dispensing (pre-authorisation) in your facility?		
	Does a physician or pharmacist review courses of therapy for specific antibiotic agents (prospective audit and feed-back) at your facility?		

Pharmacy-driven intervention	Are the following actions implemented in your facility?		
	Automated changes from intravenous to oral antibiotic therapy in appropriate situations?		
	Dose adjustment in case of organ dysfunction?		
	Dose optimisation to optimise the treatment of organisms with reduced susceptibility?		
	Automatic alerts in situations where therapy might be unnecessarily duplicative?		
	Time- sensitive automatic stop orders for specified antibiotic prescriptions?		
Diagnosis and infection specific intervention	Does your facility have specific intervention in place to ensure optimal use of antibiotics to treat the following common infections?		
	Community acquired pneumonia		
	Urinary tract infection		
	Skin and soft tissue infection		
	Surgical prophylaxis		
	Empirical treatment of MRSA		
	Non- C difficile infection (CDI) antibiotics in new cases of CDI		
	Culture proven invasive (e.g. blood stream) infections		
Tracking: monitoring antibiotic prescribing	Does your stewardship program monitor adherence to a documentation policy (dose, duration and indication)		
	Does your stewardship program monitor adherence to facility specific treatment recommendations?		
	Does your stewardship program monitor compliance with one or more of the specific interventions in place?		
	Does your facility track rates of C difficile infection?		
	Does your facility produce an antibiogram?		
	Does your facility monitor antibiotic use by one of the following?		
	By counts of antibiotics administered to patients per day (Days of therapy; DOT)?		
	By number of grams of antibiotics used (Defined daily dose; DDD)?		
	By direct expenditures for antibiotics (purchasing costs)?		

Reporting information	Does your stewardship program share facility specific reports on antibiotic use with prescribers?		
	Has a current antibiogram been distributed to prescribers in your facility?		
	Do prescribers ever receive direct, personalised communication about how they can improve their antibiotic prescription?		
Education	Does your stewardship program provide education to clinicians and other relevant staff on improving antibiotic prescribing?		
Total			