A retrospective study of antimicrobial prescribing practices in paediatric patients at the Mahalapye District Hospital, Central Botswana

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Abstract

Background

The development of antimicrobial resistance (AMR) has been linked to the increased and irrational use of antimicrobial medicines. The aim of this study was to investigate the antimicrobial prescribing practices in the paediatric medical ward at Mahalapye District Hospital (MDH) in Botswana and to determine whether antimicrobial stewardship (AMS) measures were being implemented at the hospital.

Methods

A cross-sectional, descriptive, mixed methods, observational approach was taken in this study. The study site was the paediatric medical ward (PMW) at MDH. Information about the antimicrobials prescribed for paediatric patients from January 2018 to December 2018 was collected from patients' information files and compared to national antimicrobial prescribing guidelines to determine prescribers' adherence. Qualitative semi-structured interviews were conducted with members of staff at MDH to determine whether antimicrobial stewardship (AMS) measures were adopted at the hospital.

Results

A total of 278 patients were included in this study, 12 of these were admitted twice during the study period. In total 290 admissions were analysed, with 659 antimicrobial medicines prescribed. The most common diagnoses were pneumonia (36.9%), acute gastroenteritis (20.7%), upper respiratory tract infections (3.4%), and bronchiolitis (3.1%). The most prescribed antimicrobials were ampicillin (21.4%), gentamicin (21.2%), and cefotaxime (8.3%). Adherence to guidelines was relatively good, with 82.7% of antimicrobials prescribed for the patients in the study having been prescribed in compliance with the national prescribing guidelines. The semi-structured interviews highlighted the fact that staff knew about AMS and AMR in general, however awareness of an AMS committee at MDH varied. The AMS committee was a multidisciplinary committee, which was a subcommittee of the Drugs and Therapeutics Committee (DTC).

Discussion and Conclusion

The results suggest that adherence to prescribing guidelines was relatively high compared to other paediatric antimicrobial utilisation studies in African countries. Prescribing of antimicrobial medicines was consistent with other African countries. The long period of time that it takes for microbiological test results to become available means that most prescribers rely on empirical prescribing. The antimicrobial committee is a multidisciplinary committee with defined roles for its members, consistent with international guidelines for implementing an AMS committee at a hospital.

Key words

Antimicrobial medicine

Antimicrobial stewardship

Antimicrobial resistance

Prescribing

Paediatric

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Dedication

This thesis is dedicated to my parents, for always believing in me and supporting me in everything I do.

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List of Acronyms

AGE – Acute gastroenteritis

AMR – Antimicrobial Resistance

AMS – Antimicrobial Stewardship

ASPs – Antimicrobial Stewardship Programmes

CDC – Centers for Disease Control and Prevention

DTC – Drugs and Therapeutics Committee

IDSA – Infectious Disease Society of America

GAP – Global Action Plan

GP – General Practitioner

HAI – Healthcare Acquired Infections

LMIC – Low- and Middle-Income Country

MCS – Multiple Chemical Sensitivity

MC&S – Microscopy, Culture and Sensitivity

MRSA – Methicillin-Resistant Staphylococcus aureus

MDH – Mahalapye District Hospital

MDR – Multi Drug Resistant

PMW – Paediatric Medical Ward

SAASP – South African Antimicrobial Stewardship Programme

SHEA – The Society for Healthcare Epidemiology of America

WHO – World Health Organisation

Chapter 1: Introduction

1.1 Introduction

Antimicrobials are medicines that are used for the prevention and treatment of infections caused by microorganisms. This classification includes antibacterial, antiviral, antifungal and antiparasitic medicines (Gumbo, 2018). Since the introduction of the first antimicrobials for clinical use early in the 20th century, the use of antimicrobials has been an important part of healthcare as they play a crucial role in reducing death rates from infectious diseases (Aminov, 2017; Gaynes, 2017). Some of the major advances in modern medicine have been largely supported by antimicrobials e.g., the treatment and prevention of infectious diseases; and providing prophylaxis during procedures, such as surgeries, dialysis, and dental procedures (CDC, 2019). Antimicrobials are also used to prevent infections in patients with immunocompromising conditions such as diabetes, the human immunodeficiency virus (HIV) and cancers (CDC, 2019). Antimicrobial use has not been limited to human medicine alone. Various antimicrobials have been widely used in animal health and agricultural sectors to treat and prevent infection, therefore promoting growth and increasing yield (Podolsky, 2018). Due to their success, the demand for antimicrobials has continued to increase over the years.

Sir Alexander Fleming, who discovered penicillin, one of the first antimicrobials to be used clinically, warned that the increased public demand for penicillin would result in abuse of the medicine, which would lead to the emergence of penicillin resistant microbes (Bartlett et al., 2013). Unfortunately, this development is not unique to penicillin, and the inappropriate use of antimicrobials has caused the rapid development of antimicrobial resistance (AMR) to existing antimicrobials (Fair & Tor. 2014). AMR refers to the ability of a microbe to survive in the presence of an antimicrobial (Acar & Moulin, 2012). AMR can be intrinsic or acquired. Intrinsic means the species is naturally not susceptible to the action of the antimicrobial under consideration (Acar & Moulin, 2012). AMR can also be acquired, where an antimicrobial loses efficacy against a previously susceptible species (Acar & Moulin, 2012). The acquired type of resistance is driven by the inappropriate use of antimicrobials.

The development of AMR has become a global crisis and global action is needed to preserve antimicrobial medicines (WHO, 2015a). It has been projected that if appropriate global action

is not taken, AMR could cause up to 10 million deaths worldwide by 2050 (Review on Antimicrobial Resistance et al., 2014). Organisations such as the World Health Organisation (WHO), the Society for Healthcare Epidemiology of America (SHEA), the Centers for Disease Control and Prevention (CDC) in the USA and the Federation of Infectious Diseases Societies of Southern Africa are all dedicated towards efforts to reduce AMR. The WHO's Global Action Plan on AMR highlights antimicrobial stewardship (AMS) as one of the five main objectives in its plan towards combating AMR (WHO, 2015a). One of the strategies that has been put forward by these organisations is the development and implementation of antimicrobial stewardship programmes (ASPs) in healthcare facilities (CDC, 2019).

According to Nathwani et al. (2019) antimicrobial medicines are misused in hospital settings, with about 50% of the antimicrobial prescriptions being inappropriate. They reviewed studies done in North America, Europe, Asia, Africa, South America, and Australia. ASPs are intended to aid prescribers to optimise their antimicrobial prescribing practices to get better patient outcomes and to minimise risks (CDC, 2019; WHO, 2019a).

Before an ASP is developed and implemented, the WHO recommends that a situational analysis of the facility be carried out. This can help to determine the indications for AMS for that facility (WHO, 2019a). A baseline utilisation study is recommended as part of the analysis to assess the appropriateness, extent, and quality of antimicrobial prescribing, and to determine the prescribing practices in a healthcare facility, department, or ward (WHO, 2019a). This research will study the utilisation of antimicrobials in a paediatric medical ward at a hospital in Botswana.

The background, significance, aims, and objectives are briefly outlined in this chapter.

1.2 Background to the study

1.2.1 Burden of infectious diseases in developing countries

Developing countries face a higher burden of infectious diseases compared to developed countries. According to the WHO, the number of healthy life years lost to infectious diseases in developing countries was 15 times higher than in developed countries (WHO, 2006). In 2016 infectious diseases were responsible for 29% of all the deaths globally (WHO, 2018). Africa is the only region in the world where the number of deaths from communicable diseases outweighs the number of deaths due to non-communicable diseases (Boutayeb, 2010). This is

due to the persisting burden of HIV/AIDS, malaria, tuberculosis, and other communicable diseases (Boutayeb, 2010).

1.2.2 Burden of infectious diseases in paediatric patients

Paediatric patients are frequently affected by infectious diseases (WHO, 2006). Although significant progress has been made in reducing childhood mortality rates globally, in sub-Saharan Africa childhood mortality rates remain relatively high, with 1 in 13 children dying before his or her fifth birthday (WHO, 2019b). Deaths of children under 5 are 15 times more likely to occur in sub-Saharan Africa compared to developed countries (WHO, 2019b).

Developing countries are often faced with a wide array of challenges when it comes to the prescription and use of antimicrobial medicines. These challenges include but are not limited to difficulties in diagnosing infectious diseases because of limited access to laboratories, lack of resources such as electricity, clean water supply and skilled labour in the existing laboratories (McNerney, 2015). Difficulties associated with the collection of samples from children can also impact the use of microbiological information in the prescribing of antimicrobial medicines in these patients (Bard & TeKippe, 2016). Due to these difficulties, and high mortality rates associated with infectious diseases in paediatric patients, prescribers in developing countries tend to take the empirical therapy approach rather than the definitive therapy approach, using broader spectrum antimicrobial agents (Girma et al. 2018).Studies on the prescribing of antimicrobials in paediatric patients in Eastern Ethiopia, Northern Ethiopia, Indonesia, and India showed similarities in prescribing trends e.g., ceftriaxone, gentamicin and ampicillin were among the most prescribed antibiotics (Girma et al. 2018).

1.2.3 Botswana – demographic and economic information

Botswana is a landlocked country in Southern Africa, located between South Africa, Namibia, Zambia, and Zimbabwe (World Bank, 2019). It has a relatively small population of about 2 350 000 people (United Nations Statistics Division, 2019). Botswana has experienced strong and stable economic growth since its independence in 1966 (World Bank, 2019). Its economic successes have been attributed mainly to good governance, good economic management, and its mineral wealth, which mainly consists of diamonds (World Bank, 2019). It has been classified as an upper middle-income country by the World Bank. The country is a multi-party democratic state with a stable political environment (World Bank, 2019).

Despite it being considered a developmental success story, from being one of the poorest countries in the world to achieving its current economic status, Botswana still has socioeconomic challenges. It has one of the highest income inequalities in the world, with 30% of its population living just above the poverty line (World Bank, 2019). The country's economy is dependent mainly on its minerals. Job creation is heavily dependent on state and public sector growth. Job creation has been low (World Bank, 2019). While the country's education expenditure is significant this has not translated into a more skilled workforce being produced. Although about 9% of Botswana's GDP is spent on education, and public primary education is free, unemployment rates remain high at 17.7% (World Bank, 2019). High unemployment rates have previously been linked to worsened health states. This includes increases in infectious disease incidence due to factors such as poor living conditions and less access to healthcare or adequate treatment (Suhrcke et al., 2011).

1.2.4 AMS in Botswana

In Botswana, efforts are being made to reduce the irrational prescribing and use of antimicrobial agents. The amendment of the Botswana Antimicrobial Therapy Guidelines in 2012 included suggestions aimed at improving the prescribing and utilisation of antimicrobials. Several private hospitals in Botswana have developed ASPs which are facilitated by multidisciplinary AMS teams (Massele et al. 2017). This is in line with recommendations by the WHO for encouraging the rational use of antimicrobials in hospitals (WHO, 2015a). These hospitals have reported the use of guidelines, formulary restriction and antibiograms to have been effective in improving the rational prescribing and use of antimicrobials (Massele et al. 2017). However, there is little data that supports the evaluation of the interventions being implemented and the impact of such interventions on the utilisation of antimicrobials in these hospitals. Despite the efforts being made towards promoting the rational use of antimicrobials in Botswana, there are still concerns regarding the availability of, and the adherence to, guidelines in private and public healthcare institutions (Massele et al., 2017; Paramadhas et al., 2019).

1.3 Significance of the study

Low- and middle-income countries, particularly in sub-Saharan Africa bear a higher burden of infectious diseases compared to other regions in the world (Boutayeb, 2010). Due to this burden of infectious diseases, childhood mortality due to infectious diseases is highest in the sub-

Saharan Africa region (WHO, 2019b). The high incidence of infectious diseases is one of the drivers of the use of antimicrobial medicines (Miller-Petrie et al., 2017). The use of antimicrobials has been causally linked to the development of resistance among pathogens(WHO, 2015a).

The Global Action Plan (GAP) on AMR was put forward by the WHO and outlines 5 major objectives to tackle AMR. Objective 2 of the GAP is aimed at "strengthening the knowledge and evidence base through surveillance and research" (WHO, 2015a). Surveillance and research into antimicrobial utilisation behaviours, antimicrobial resistance patterns and prescribing practices is essential in the effort to tackle AMR (WHO, 2015a). Knowledge gaps exist about the incidence, prevalence and spread of AMR across different pathogens and geographical locations (WHO, 2015a). It is also important to understand how resistance develops and spreads and further research is needed in these areas. Research is also needed to understand prescribing behaviours and to support effective ASPs in human and animal health and agriculture (WHO, 2015a, 2019a).

Objective 4 of the WHO GAP highlights the need "to optimize the use of antimicrobial medicines in human and animal health" (WHO, 2015a). Despite efforts being made around the world to reduce the use of antimicrobial medicines, use thereof is still increasing. AMS in human and animal health is recommended to reduce the inappropriate and unnecessary use of antimicrobials (WHO, 2015a). Healthcare facilities, particularly hospitals are some of the major targets for AMS due to the high use of antimicrobials in these settings (Nathwani et al., 2019; WHO, 2019a).

Studies carried out in sub-Saharan countries have shown that antimicrobial medicines have been used inappropriately. For example, a study in Ghana showed high antimicrobial use in paediatric patients in the 10 hospitals that were studied and noted the inappropriate use of third generation cephalosporins as a major target for future AMS programmes (Labi et al., 2018). Another study carried out at a hospital in Gambia reported that more than half of the paediatric patients admitted during the study period received antimicrobial medicines despite no microbiological evidence for their indication, which pointed to high occurrences of empirical prescribing (Chaw et al., 2018).

In Botswana, studies have been carried out to investigate the prescribing and use of antimicrobial medicines in ambulatory care (Boonstra et al., 2005; Mashalla et al., 2017). Few studies have been carried out to investigate the appropriateness of antimicrobials in hospital

settings (Fisher et al., 2009; Paramadhas et al., 2019) A study carried out by Fisher et al (2009) at a referral hospital in Botswana reported that although the initiation of antimicrobial medicines was found to be reasonable in most of the prescriptions , the duration of treatment tended to be lengthy. A more recent study carried out in 10 hospitals (9 public and 1 private) in Botswana reported high rates of: antimicrobial use (70.6%), empirical prescribing and use of parenteral formulations of antimicrobials among 711 patients (Paramadhas et al., 2019). Data on appropriateness of antibiotic prescribing in Botswana seems to be lacking.

Botswana is one of the countries where there is little surveillance data on the incidence of AMR and the implementation of ASPs (WHO, 2018). According to data submitted to the WHO Global Database for Antimicrobial Resistance Country Self-Assessment for 2017-2018, no data was provided by Botswana about the progress of a national action plan on AMR and the existing national infection prevention and control programmes were not fully implemented (WHO, 2018). Although some effort is being made to reduce the irrational use of antimicrobial medicines in Botswana, few studies have reported on AMR, the use of antimicrobial medicines or the implementation of ASPs in hospitals in Botswana (Paramadhas et al., 2019). In order to effectively optimise the use of antimicrobial medicines in human health, research needs to be done both at an institutional level and a national level to determine current practices in prescribing of antimicrobial medicines and decide on appropriate interventions (WHO, 2019a). The paucity of data regarding antimicrobial use in Botswana, specifically in paediatric patients, inspired this research.

This study was carried out to determine a baseline of the prescribing practices and utilisation of antimicrobial medicines in paediatric in-patients at a hospital in Botswana. Patient information files were studied to determine prescribers' compliance with antimicrobial prescribing guidelines. Healthcare staff were interviewed to determine current AMS interventions being implemented at the hospital and possible factors influencing prescribing of antimicrobial medicines to paediatric in-patients. The study outcomes were used to comment and make recommendations to the hospital regarding the prescribing and use of antimicrobial medicines in the paediatric ward.

1.4 Aims and objectives.

The aim of this study was to investigate the antimicrobial prescribing practices in the paediatric medical ward in the Mahalapye District Hospital (MDH), a government funded district hospital

situated in Mahalapye, a town in the Central District of Botswana and to determine whether antimicrobial stewardship (AMS) measures were being implemented at the hospital.

The study determined whether antimicrobial medicines were prescribed and used rationally according to the guidelines followed at MDH and whether antimicrobial stewardship measures were being implemented in the paediatric medical ward.

The specific objectives of the study include the following:

- To determine which antimicrobial prescription guidelines were used when prescribing antimicrobials for paediatric patients in the Mahalapye District Hospital (MDH).
- To evaluate the prescribers' compliance to the identified guidelines in their practice by retrospectively assessing prescriptions in patient records.
- To determine the factors that influence prescribing practices with respect to antimicrobials in the paediatric medical ward.
- To establish whether the MDH has an ASP in place, and if so, determine the personnel involved, the AMS guidelines used, and the level of support the programme receives from the institution's administration.
- To determine possible interventions for antimicrobial prescribing and stewardship at MDH.

1.5 Overview of chapters

Chapter 1 introduced the study and explained the study background, the significance of the study and the aims and objectives of the study.

Chapter 2 is the literature review. In this chapter, the origins and effect of AMR, AMS strategies and interventions, AMS in developed and developing countries, and AMR and AMS in paediatric patients are discussed. Baseline antimicrobial utilisation studies are also discussed.

Chapter 3 describes the methodology used in this study. It describes the data collection and analysis process and the tools used to do this. Ethical considerations and permission to conduct the study are discussed in this chapter.

Chapter 4 contains the findings of the study.

Chapter 5 provides a discussion of the research findings and evaluates them in relation to the available literature. Bias and limitations of the study are discussed in this chapter.

Chapter 6 summarizes the major findings of the study and offers recommendations for further research.

Chapter 2: Literature Review

2.1 Introduction

Although this research focuses on the application of AMS in a particular context it is useful to include a brief overview of the following: different types of antimicrobial medicines, the mechanisms of antimicrobial resistance, the development of AMR, responses to AMR, previous and current antimicrobial stewardship (AMS) strategies in high and low- to middle income countries, and AMR in paediatric patients globally and in the context of Botswana.

2.2 Antimicrobial medicines

Antimicrobial medicines are an important class of medicines, and their use affects both the treated individual and the community (Dyar et al., 2017). The misuse of antimicrobial medicines has been linked to the development of antimicrobial resistance through the natural response mechanisms of microorganisms to environmental stresses (Munita et al., 2016). Infections resistant to antimicrobials have been associated with increased morbidity and mortality, increased length of stay in hospital and increased healthcare costs (Friedman et al., 2016; Frieri et al., 2017).

2.2.1 History of antimicrobial medicines

The use of antimicrobial medicines began with a historically significant breakthrough in medicine. The discovery of penicillin by Sir Alexander Fleming in 1928 meant that treating bacterial infections, which were previously incurable, had become a possibility (Gaynes, 2017). Penicillin was later developed into a medicine that could kill bacteria in vivo, and this changed the course of medicine significantly (Gaynes, 2017). In the early 1930s, a group of scientists, which included German pathologist and biologist named Gerhard Domagk, discovered that chemical derivatives from the azo-dye Prontosil had bacteriological activity. This led to the production of sulphanilamide and other sulpha-derivative antimicrobials (Wainwright & Kristiansen, 2011).

These developments in medicine meant that previously life-threatening bacterial infections such as smallpox, cholera, diphtheria and pneumonia could be treated with antimicrobial medicines. Since then, antimicrobial medicines have been widely produced and used around

the world. They have aided in preventing loss of life from infections and have made it safer to perform surgical procedures, transplantations, and other invasive procedures. These medicines also help to prevent infections in situations where the immune system may be compromised, such as in HIV positive patients (NHS, 2019). All these developments are being threatened by the increased emergence of antimicrobial resistant infections (Fair & Tor. 2014).

2.2.2 Uses of antimicrobial medicines in human health

The following section provides examples of antimicrobial medicines, a brief summary of their modes of action, and their applications in human healthcare.

Antimicrobial medicines are used widely in human and animal health. This study focuses on human healthcare, therefore information on the agricultural aspect of antimicrobial use was not included.

2.2.2.1 Inhibitors of cell wall synthesis

The bacterial cell wall is made up of alternating *N*-acetylglucosamine (NAG) and *N*-acetylmuramic acid (NAM) molecules joined by covalent bonds to make glycan chains, and these adjacent glycan chains are linked to each other by tetrapeptide chains to create peptidoglycan (Cho et al., 2014). Many antibacterial agents such as β-Lactams and glycopeptides target the synthesis of these peptidoglycan cell walls, which results in cell lysis. Antibacterial medicines that act in this way are bactericidal (Cho et al., 2014; Hooper et al., 2015).

β-Lactams

β-Lactams are bactericidal and act by inhibiting cell wall synthesis by interfering with the transpeptidase enzymes involved in crosslinking stem-peptide chains which form peptidoglycan (Cho et al., 2014). Benzylpenicillin and phenoxymethyl-penicillin are susceptible to β-Lactamase action and have a narrow spectrum of activity. They are active against many gram-positive bacteria and anaerobic organisms. They have limited effectiveness against gram-negative bacteria(Rossiter et al., 2016).

Broader spectrum penicillins such as ampicillin and amoxycillin are active against many gram-positive and gram-negative bacteria (Pandey & Cascella, 2021). However, while some of them have some resistance, these penicillins are also susceptible to β-Lactamases. The combination of broad spectrum, β-Lactamase susceptible antibiotic agents with β-Lactamase inhibitors

increases the antimicrobial's effectiveness and spectrum of activity (Pandey & Cascella, 2021). Examples include the combination of amoxycillin with clavulanic acid, and piperacillin with tazobactam (Pandey & Cascella, 2021).

There are also narrow-spectrum penicillins with β-Lactamase resistance. These include cloxacillin, flucloxacillin and methicillin (Holten & Onusko, 2000). These agents have limited activity against gram-positive bacteria and no activity against almost all gram-negative bacteria (Holten & Onusko, 2000).

Another group of β-Lactam antibiotics is the cephalosporins. Cephalosporins are effective against gram-positive and gram-negative bacteria (Bui & Preuss, 2021). There are five generations of cephalosporins. First generation cephalosporins are active against gram-positive cocci and can be used to treat staphylococcal and streptococcal infections of the skin and soft tissue (Holten & Onusko, 2000). Examples include cefazolin, cephalexin and cephradine (Holten & Onusko, 2000).

Second generation cephalosporins include cefaclor and cefuroxime (Bui & Preuss, 2021). These agents are active against gram-positive cocci and certain gram-negative bacilli (Chaudhry et al., 2019). Cephamycins like cefoxitin are usually classed in this group and are active against gram-negative anaerobes (Chaudhry et al., 2019). Second generation cephalosporins and cephamycins can be used to treat respiratory tract infections such as pneumonia, as well as genitourinary tract infections, blood stream infections and otitis media (Chaudhry et al., 2019).

Third generation cephalosporins include cefotaxime, cefpodoxime, ceftriaxone and ceftazidime, and active against Haemophilus influenzae and some Enterobacteriaceae (Bui & Preuss, 2021). This class of antimicrobials can be used to treat meningitis, skin and soft tissue infections and hospital acquired bacteria pneumonia (Chaudhry et al., 2019).

Fourth generation cephalosporins are active against gram-positive cocci and gram-negative bacilli (Chaudhry et al., 2019). Cefepime and cefpirome are two antibiotics in this group of antibiotics (Bui & Preuss, 2021).

Fifth generation cephalosporins are active against gram-positive and gram-negative bacteria (Bui & Preuss, 2021). Ceftaroline is a fifth generation cephalosporin which is active against Methicillin-resistant S. aureus (MRSA) and β-Lactamase-producing Enterococeus faecalis (Bui & Preuss, 2021).

Glycopeptides and Lipoglycopeptides

Glycopeptides and lipoglycopeptides are bactericidal and inhibit bacterial cell wall synthesis by inhibiting the integration of amino acids into peptidoglycan (Zeng et al., 2016). They bind to the d-alanyl-d-alanine terminus of the peptidoglycan precursor, which prevents polymerisation of the NAG-NAM units (Zeng et al., 2016). This action interrupts the formation of the peptidoglycan wall and results in cell lysis (Zeng et al., 2016). Glycopeptides also interact with the lipid bilayer of the bacterial cell membrane, which stabilises the interaction of the glycopeptide antibiotic with the bacterial cell and is beneficial for antimicrobial action (Zeng et al., 2016). These medicines are only active against Gram-positive bacteria (Rossiter et al., 2016). Vancomycin can be used in paediatric patients to treat MRSA infections, sepsis and catheter related infections (Minotti et al., 2021).

Bacitracin and Fosfomycin

These bactericidal antibacterial medicines interfere with processes that produce the precursors of peptidoglycan in the cytoplasm (Hooper et al., 2015).

2.2.2.2 Inhibitors of protein synthesis

Bacterial ribosomes differ enough from eukaryotic ribosomes to allow for selective antibacterial targeting (Hooper et al., 2015). Antibacterial medicines that inhibit protein synthesis target these bacterial ribosomes (Hooper et al., 2015).

Aminoglycosides

These antibacterial agents are bactericidal (Hooper et al., 2015). They act by binding irreversibly to bacterial 16S ribosomal RNA (rRNA) of the 30S ribosomal subunit, which, at low concentrations results in misreading of messenger RNA (mRNA) which causes incorrect amino acids to be added to the peptide chain, and at high concentrations blocks the translocation of the peptide chain (Krause et al., 2016). Aminoglycosides can be used in paediatric patients for the treatment of infections such as early-onset sepsis and pulmonary infections in children with cystic fibrosis (McWilliam et al., 2017).

Tetracyclines and Glycylcyclines

This class of antibacterial medicines is bacteriostatic (Grossman, 2016). Tetracyclines inhibit bacterial protein synthesis by binding reversibly to the 16S rRNA of the 30S ribosomal subunit in the microorganism - an action which results in the prevention of peptide elongation

(Grossman, 2016). Tigecycline is a semi-synthetic glycylcycline which is derived from and has a similar mechanism of action to tetracyclines (Grossman, 2016; Hooper et al., 2015). It is however able to evade mechanisms of resistance that affect most tetracyclines due to structural modifications that increase tigecycline's affinity to the ribosomal binding sites (Bauer, 2004; Grossman, 2016). However, despite this, there have been reports of tigecycline resistance emerging in microorganisms such as *S. pneumoniae, S. aureus, Enterobacter* and *Acinetobacter* species (Sun et al., 2013). Tetracyclines are contraindicated in children below 8 years old as they are associated with tooth discolouration in this group (Pöyhönen et al., 2017).

Macrolides, Ketolides and Streptogramins

These bacteriostatic antibacterial agents bind to the 23S rRNA of the 50S ribosomal subunit and block translocation of the peptide chain (Fyfe et al., 2016). Erythromycin can be used in paediatric patients for the treatment of lower respiratory tract infections, pertussis and diphtheria (Klein, 1997).

Lincosamides

Clindamycin is the only agent in this class available for clinical use. It binds to the 23S rRNA of the 50S ribosomal subunit and blocks the formation of peptide bonds and is bacteriostatic (Hooper et al., 2015).

Chloramphenicol

Chloramphenicol is bacteriostatic (Hooper et al., 2015). It binds reversibly to the 23S rRNA of the 50S ribosomal subunit and causes the improper positioning of aminoacyl tRNA in the A site, which disrupts peptide chain formation (Arenz & Wilson, 2016; Hooper et al., 2015). The use of chloramphenicol in neonates may cause toxicity resulting in grey baby syndrome in neonates and it is therefore contraindicated in this age group (Oong & Tadi, 2021).

Oxazolidinones

Linezolid is a bacteriostatic antibiotic that is effective against Gram-positive bacteria, and it acts by binding to the A site on the 23S rRNA of the 50S ribosomal subunit and preventing bacterial protein synthesis (Arenz & Wilson, 2016; Hooper et al., 2015). Linezolid can be used as a treatment for drug-resistant tuberculosis in paediatric patients (Garazzino & Tovo, 2011).

Mupirocin

Mupirocin is a topical bacteriostatic agent that inhibits bacterial protein synthesis by competing with isoleucine and binding to isoleucyl tRNA synthetase, which reduces the concentration of isoleucyl tRNA, therefore inhibiting the synthesis of new bacterial cells (Hooper et al., 2015). Mupirocin can be used for the treatment of skin conditions such as impetigo in paediatric patients (Rossiter et al., 2016).

2.2.2.3 Inhibitors of bacterial metabolism

Inhibitors of bacterial metabolism usually target the folate synthesis mechanism in bacteria (Hooper et al., 2015). Mammalian cells do not produce folate on their own, and rely on external sources, therefore these antibacterial medicines can act selectively on bacterial cells (Hooper et al., 2015). Folate is essential in the synthesis of nucleic acids and amino acids that are essential for bacterial cell growth and replication (Hooper et al., 2015). Two folate synthesis pathways are targeted.

Sulphonamides

These antibacterial agents are bacteriostatic. They hinder bacterial cell growth by inhibiting dihydropteroate synthetase (DHPS), an action which inhibits bacterial synthesis of folate (Kapoor et al., 2017).

Trimethoprim

This bacteriostatic antibacterial blocks dihydrofolate reductase (DHFR), which is part of the folate synthesis pathway (Kapoor et al., 2017). It is usually used in combination with sulfamethoxazole (a sulphonamide) due the wide-spread resistance to it among Gram-negative bacteria (Kapoor et al., 2017; Rossiter et al., 2016). When sulfamethoxazole and trimethoprim are used together, the effect of the combination becomes bactericidal due to the synergistic effect in their mechanisms of action.

2.2.2.4 Inhibitors of DNA and RNA synthesis or activity

DNA and RNA are essential for bacterial reproduction and multiplication. Agents that affect bacterial DNA and RNA can affect bacterial growth and therefore exert an antimicrobial effect.

Quinolones

These antibacterial agents are bactericidal (Hooper et al., 2015). They inhibit DNA gyrase and DNA topoisomerase IV, which are essential in the reproduction of bacterial DNA and are responsible for catalysing negative supercoiling of double-stranded DNA and unlinking daughter chromosomes following DNA replication, respectively (Rossiter et al., 2016). They inhibit DNA replication, and cause double breaks in DNA strands, which is bactericidal (Hooper et al., 2015). Mammalian DNA gyrase and DNA topoisomerase IV are structurally different to those of bacterial cells, thus, quinolones act selectively on bacterial cells (Hooper et al., 2015). The use of fluoroquinolones has been limited in paediatric patients due to the possibility of arthropathy resulting from their use in this group (Adefurin et al., 2011).

Rifamycins

These bactericidal rifamycin B derivatives selectively bind to bacterial RNA polymerase and block the elongation of bacterial mRNA (Rothstein, 2016). This agent can be used in the treatment of tuberculosis in paediatric patients and adults (Rossiter et al., 2016).

Nitrofurantoin and Metronidazole

Nitrofurantoin is a nitrofuran derivative that is thought to cause breakage in bacterial DNA strands through the formation of highly reactive derivatives that are formed when it is reduced by bacteria and its effect is bactericidal (Hooper et al., 2015). Nitrofurantoin can be used in paediatric patients for the treatment of urological infections such as UTIs (Williams et al., 2019).

The action of metronidazole is facilitated by anaerobic bacteria that are involved in a reduction reaction which produces reactive derivatives of metronidazole that damage bacteria DNA (Hooper et al., 2015). This action is bactericidal. Both metronidazole and nitrofurantoin are prodrugs and are selective for bacteria because the reduction reaction that occurs can only be facilitated by certain bacterial cells (Hooper et al., 2015).

2.2.2.5 Disruptors of membrane integrity

Both the cytoplasmic membrane and the outer membrane (relative to gram-negative bacteria) are important for bacterial survival.

Polymyxins

The mechanism of action of these bactericidal antimicrobials is unclear. These cationic cyclic polypeptides are thought to disturb both the cytoplasmic membrane and the outer membrane in gram-negative bacteria (Hooper et al., 2015; Trimble et al., 2016). There is evidence to suggest that they also affect cell division, and might bind to ribosomes and inhibit bacterial respiration (Trimble et al., 2016).

Daptomycin

This bactericidal agent targets gram-positive bacteria. In the presence of calcium, daptomycin binds to the cytoplasmic membrane via the anionic phospholipid phosphatidylglycerol and causes leakage of cytoplasmic potassium ions through the formation of pores and results in membrane depolarisation (Hooper et al., 2015; Miller et al., 2016).

2.3 Antimicrobial resistance

The increase in incidence of antimicrobial resistance to commonly used antimicrobial medicines is a threat to global health and modern medicine as we know it. Infections resistant to antimicrobials are claiming a large number of lives globally every year. Resistant infections are projected to cause at least 10 million deaths by the year 2050 (Review on Antimicrobial Resistance, 2014). The number of new antimicrobials developed has decreased significantly, with few antimicrobial medicines in the drug development pipeline, and even fewer new classes offering different mechanisms of action (WHO, 2017).

Microorganisms such as bacteria, viruses, fungi, and protozoa are highly adaptable genetically, which allows them to withstand many environmental threats such as the presence of antimicrobials (Davies & Davies, 2010). Antimicrobial resistance is a natural result of a microorganism's interaction with the environment. In some organisms, there are inherent properties such as the presence of an outer membrane, which naturally protects these organisms from antimicrobial agents (Arzanlou et al., 2017). They are classified as being intrinsically resistant to one or multiple antimicrobials. Organisms can also become resistant to antimicrobials through their ability to adapt and survive under the stress conditions that result from exposure to antimicrobials (Arzanlou et al., 2017). This is called adaptive resistance. Antimicrobial resistant properties can also be acquired, where a susceptible organism acquires resistance genes from other organisms or through genetic mutations (Munita et al., 2016). Intrinsically resistant microorganisms are not the focus of the antimicrobial resistance problem

that the world is currently facing as these organisms would have already been resistant to certain antimicrobials prior to being exposed to them. Antimicrobial resistance in this context refers to the adaptive and acquired resistance in disease-causing microorganisms that were initially susceptible to the antimicrobial compound (Munita et al., 2016). Therefore, these two resistance mechanisms warrant further discussion.

2.3.1. Genetics of antimicrobial resistance

Exposure to antimicrobial medicines can result in some genetic changes in microorganisms that could lead to antimicrobial resistance.

2.3.1.1 Genetic mutation

When a microorganism is exposed to an antimicrobial agent to which it is susceptible, a genetic mutation may occur in the microorganism. This mutation changes the way that the antimicrobial can act on the microorganism, which allows it to survive in the presence of the antimicrobial (Davies & Davies, 2010). The genetic mutations that result in antimicrobial resistance usually involve one of the following changes:

i. alteration of the antimicrobial target;
ii. decrease in uptake of the antimicrobial into the bacterial cell;
iii. initiation of an efflux mechanism to expel the antimicrobial molecules; or
iv. modification of regulatory pathways, thus, altering major metabolic pathways. (Munita et al., 2016).

2.3.1.2 Horizontal gene transfer (HGT)

Most antimicrobials used clinically either occur in nature or were derived from naturally occurring compounds. Exposure to these naturally occurring antimicrobials has – over time - allowed microorganisms to develop antimicrobial resistance. Such microorganisms are the basis for HGT, as their resistant properties can be transferred to susceptible microorganisms (Munita et al., 2016).

Microorganisms can obtain resistant genes from other microorganisms through one of the following mechanisms:

i. conjugation,
ii. transduction, or
iii. transformation (Munita et al., 2016).

Conjugation requires contact between the donor cell and the recipient cell to transfer genetic material (Riedel et al., 2019a). Mobile genetic elements, such as plasmids are used to transport DNA between cells (Riedel et al., 2019a). This type of HGT is associated with antimicrobial resistance in hospital environments (Munita et al., 2016). It is also believed to be responsible for transfer of antimicrobial resistant genetic material in the gastrointestinal tract (Munita et al., 2016).

Transduction involves the transfer of DNA in a phage-encoded protein coat. This type of HGT is responsible for transferring pathogenicity from pathogenic cells to benign ones, as seen in *V. cholerae* (Riedel et al., 2019a).

Transformation involves the transfer of naked DNA that is not connected to any molecules, such as lipids or proteins, into the receptor cell, which makes it simpler, compared to the other mechanisms of gene transfer (Munita et al., 2016). This form of HGT has been studied well in laboratory conditions, however, there is little proof of AMR mediated by this mechanism naturally (Lerminiaux & Cameron, 2019).

Other mobile elements called integrons, transposable elements and gene cassettes are also involved in the passing of resistant genetic material between cells. These elements work by integrating themselves into plasmids, and in that way, they can be transferred from donor cells to receptor cells (Gumbo, 2017). They facilitate antimicrobial resistance either by functioning as integration sites for elements that encode resistance, or by encoding antimicrobial resistance themselves, as is the case for integrons (Gumbo, 2017).

2.3.2 Mechanisms of resistance

Microorganisms have - over time - developed complex mechanisms of resistance involving many different biochemical pathways (Davies & Davies, 2010). Multiple pathways may exist in a single cell of a microorganism, which provides the microorganism with greater protection against the antimicrobial (Munita et al., 2016). These mechanisms may come about as a result of some of the genetic changes discussed above. Although the precise mechanisms of antimicrobial resistance are complex and probably not fully understood yet, they seem to involve processes that:

i. alter the antimicrobial molecule,
ii. prevent access of the antimicrobial to its targets,
iii. adapt the cellular environment to withstand the effects of the antimicrobial, or

iv. alter or protect the antimicrobial's target (Arzanlou et al., 2017; Kapoor et al., 2017; Munita et al., 2016). These mechanisms are discussed in the following section.

2.3.2.1 Alteration of the antimicrobial molecule

Chemical alteration of the antimicrobial

Microorganisms can produce enzymes that modify the antimicrobial molecule chemically. This affects the antimicrobial's efficacy, usually by reducing the molecule's affinity for its target site (Munita et al., 2016). This type of resistance mechanism can be seen in bacterial species such as *Providencia stuartii*, mycobacteria and Methicillin-resistant *Staphylococcus aureus* (MRSA), mediated by enzymes called aminoglycoside-modifying enzymes (AMEs), which covalently bind to the aminoglycoside molecule resulting in the acetylation, phosphorylation or adenylation of the molecule (Khosravi et al., 2017; Ramirez & Tolmasky, 2010). The types of AMEs present, the aminoglycosides they affect, and the form and extent of their effect can vary between species.

Destruction of the antimicrobial

An example of this type of resistance is seen in resistance to β-Lactams, where β-Lactamase enzymes deactivate the antimicrobial molecule by destroying the amide bond in the β-Lactam ring (Kapoor et al., 2017). The rise in β-Lactamase mediated AMR soon after the introduction of penicillin to the public market posed a significant threat to the sustainability and efficacy of this medicine. As infections caused by penicillin-resistant *Staphylococcus aureus* spread, a penicillinase (which is a type of β-Lactamase enzyme) was found to be the cause of resistance (Saga & Yamaguchi, 2009). In order to mitigate the resistance problem, new β-Lactam antibiotics were developed, which are less susceptible to penicillinases and have a broader spectrum of activity, such as ampicillin. However, microorganisms continued to develop new mechanisms of resistance to the newly developed antimicrobials. In 1960, a new β-Lactamase, which was named TEM-1, was discovered and was able to hydrolyse ampicillin (Fernandes et al., 2013).

The introduction of third generation cephalosporins in 1980, which were not vulnerable to known β-Lactamases at the time, was hailed as a breakthrough in the fight against AMR (Paterson & Bonomo, 2005). However, this was short-lived as extended-spectrum β-Lactamases (ESBLs) were soon discovered and these were capable of hydrolysing first, second and third generation cephalosporins (Paterson & Bonomo, 2005). Another β-Lactamase, NDM-

1, which is capable of inactivating carbapenems, was also discovered in 2008 (Arzanlou et al., 2017; Moellering, 2010).

2.3.1.2 Prevention of access of the antimicrobial to its target site

Many antimicrobial medicines have targets inside the cell of the microorganism. They need to be able to penetrate the cell wall and cell membranes of the microorganisms to reach their targets and exert their effects (Gumbo, 2017).

Decrease in cell permeability

Microorganisms can reduce uptake of an antimicrobial by reducing cell permeability to the antimicrobial molecules. Hydrophilic antimicrobial molecules are particularly affected by this resistance mechanism (Kumar & Schweizer, 2005). Since most cell membranes are largely made up of lipids, the hydrophilic antimicrobials, such as β-Lactams and fluoroquinolones, rely on hydrophilic channels, called porins to enter the microorganism cells (Gumbo, 2017). Uptake of antimicrobials can be reduced either by reducing the number of porins or changing the type and function of the porins present in the cell membrane (Kumar & Schweizer, 2005).

Production of efflux pumps

Microorganisms, usually bacteria, can develop mechanisms that expel substances that are toxic to them from their cells by producing efflux pumps from protein constituents (Poole, 2005). It is through these mechanisms that some microorganisms develop resistance to antimicrobial medicines. Antimicrobials that are affected by this resistance mechanism include fluoroquinolones, tetracyclines, macrolides, carbapenems, and β-Lactams (Poole, 2005).

2.3.1.3 Alteration of the antimicrobial target site

Protection of the target site

This mechanism has been seen in tetracycline and fluoroquinolone resistance. In tetracycline resistance, the microorganism cell produces proteins (TetM and TetO) that dislodge the tetracycline molecule from its target and prevents it from rebinding to the target again (Roberts, 2005).

In fluoroquinolone resistance, microorganisms produce the quinolone resistance protein Qnr, which competes with fluoroquinolones for their target site, preventing them from having an effect (Redgrave et al., 2014).

Modification of the target site

Mutations of the target sites in microorganism cells may result in reduced affinity of the antimicrobial for its target site or alter the structure of the target site which both affect the binding of the antimicrobial molecule to its target site (Arzanlou et al., 2017). This type of mechanism has been seen in rifampicin, fluoroquinolone, macrolides, and oxazolidinone resistance (Munita et al., 2016).

Microorganisms can also develop resistance by producing alternatives to the antimicrobial targets which perform the same function. β -Lactam resistance can develop this way, where the microorganism can obtain an external gene which encodes for an alternative PBP (PBP2), which performs the same function as PBP but has low affinity for β-Lactam antimicrobials (Reygaert, 2018). Another example of this type of resistance is where vancomycin resistance is achieved in enterococci by developing an alternative biochemical method for the synthesis of peptidoglycan.

Lastly in this class of mechanisms of resistance, the microorganism can develop resistance by increasing production of the antimicrobial target, which overwhelms the antimicrobial and bypasses its effect (Munita et al., 2016). Trimethoprim-sulfamethoxazole exerts its effect by inhibiting bacterial folate synthesis (Gumbo, 2017) through inhibition of the dihydropteroic acid synthase (DHPS) and dihydrofolate reductase (DHFR) enzymes, respectively. Resistance to this antimicrobial can be achieved by increasing the production of these enzyme targets (Munita et al., 2016).

2.4 Antimicrobial stewardship

The spread of AMR can be combatted by implementing antimicrobial stewardship, which can be implemented at both a national and an institutional level.

The Infectious Diseases Society of America (IDSA) defines AMS as "coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents by promoting the selection of the optimal antimicrobial drug regimen including dosing, duration of therapy, and route of administration" (Fishman, 2012, p. 323). It further outlines the objectives of AMS as follows:

- To achieve the most favourable clinical outcomes where antimicrobial medicines are utilised.

- To reduce the adverse effects associated with the use of antimicrobial medicines, including the emergence of antimicrobial resistance; and
- To reduce costs associated with inappropriate use of antimicrobial medicines. (Fishman, 2012)

A review by Dyar et al (2017) found that there are many definitions for AMS and proposed that AMS could be defined as "a coherent set of actions which promote using antimicrobials in ways that ensure sustainable access to effective therapy for all who need them" and proposed as a strategy towards fighting AMR.

The IDSA definition of AMS focuses on the role of prescribers to optimise antimicrobial therapy for individual patients. Both definitions and the IDSA objectives emphasise the need for coordinated action by both prescribers and non-prescribers to ensure the appropriate and sustainable use of antimicrobial medicines. They encompass the responsibility of prescribers to work towards achieving good clinical outcomes for the individual patients in their care, as well as the societal responsibility of all individuals to behave in a way that promotes the continued availability of efficacious antimicrobial medicines.

The next part of the literature review explores the different AMS strategies and how they can be implemented with the aim of further defining the study context and motivation for the research.

2.4.1 Organisational efforts towards stewardship

The WHO has called the scourge of antimicrobial resistance a public health emergency and global action is required to combat the increasing prevalence of resistance (Review on Antimicrobial Resistance, 2014). The world needs to employ strategic approaches to improve the use of antimicrobials to avert resistance and improve healthcare outcomes for patients. Strategies need to also be implemented in the animal health and food production industries as resistance can also emerge due to poor antimicrobial practices in these sectors. These strategic approaches are collectively referred to as Antimicrobial Stewardship (AMS).

The Global Action Plan (GAP) on Antimicrobial Resistance mentioned in chapter 1, was developed by the WHO, in an effort to combat the increase in AMR. This plan outlines five main objectives that are aimed at optimising the use of antimicrobial medicines and minimising resistance (WHO, 2015a). According to the GAP, ASPs need to:

(1) “improve awareness and understanding of antimicrobial resistance through effective communication, education and training.
(2) strengthen the knowledge and evidence base through surveillance and research.
(3) reduce the incidence of infection through effective sanitation, hygiene, and infection prevention measures.
(4) optimise the use of antimicrobial medicines in human and animal health; and
(5) develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment into new medicines, diagnostic tools, vaccines and other interventions” (WHO, 2015a, pp. 8–11).

These five objectives can be applied by countries to develop their own nation action plans on AMR in line with WHO recommendations (WHO, 2015a). The WHO GAP objectives are discussed in the following section.

2.4.1.1 WHO GAP objectives

Objective 1: Improve awareness and understanding of antimicrobial resistance through effective communication, education, and training.

A WHO situational analysis performed in WHO regions worldwide showed low AMR awareness amongst the public in all WHO regions, and amongst healthcare professionals in some of the WHO regions (WHO, 2015b). For example, data in the African region showed that there was low awareness of AMR in both the public and healthcare sectors. The WHO study only included information from 17% of the member countries, therefore, these results may not have been reflective of the entire region. However, the study concluded that the data showed that AMR is an increasing problem in the African region. The data for this study was collected by means of a questionnaire, which was given to the countries’ authorities to complete. (WHO, 2015b)

Research has been carried out to evaluate the knowledge and attitudes towards AMR amongst healthcare professionals and medical students. Studies done in the USA, Europe and South Africa have shown some significant similarities in the attitudes and perceptions of medical students towards antimicrobial medicines. Across all the universities evaluated, AMR was recognised as an important problem in healthcare nationally and globally (Abbo et al., 2013; Dyar et al., 2014; Wasserman et al., 2017). In the literature reviewed it seemed that most medical students believed that AMR was a national problem, but fewer students believed that it was a problem in the hospitals that they had worked in (Abbo et al., 2013; Wasserman et al.,

2017). This suggests that there may be a lack of ownership of responsibility towards AMR among medical students. This presents a possible challenge in the implementation of AMS measures as it may be difficult to change the behaviours of prescribers if they do not believe that their prescribing practices may contribute to AMR.

In order to improve prescribing practices, prescribers need to be well informed on the subject of antimicrobial medicines and AMR. Research conducted to determine the knowledge and perceptions of medical students in Europe and in the USA about AMR showed that there was insufficient understanding and awareness amongst medical students (Abbo et al., 2013; Dyar et al., 2014). Knowledge scores showed that the medical students had poor knowledge of factors such as the incidence of AMR, its burden of disease, how to interpret antibiograms and mechanisms of antimicrobial resistance. Adjustments to the current curricula in medical schools and the methods of delivering information are a crucial consideration that need to be made for the education to be impactful (Abbo et al., 2013; Dyar et al., 2014; Wasserman et al., 2017). The influence of technology should be taken into account when developing teaching methods, and it may be advantageous to incorporate new teaching and learning methods that present "real world" scenarios for students to get accustomed to making prescribing decisions (Abbo et al., 2013). For example, students reported that they were using different sources of information such as Wikipedia, textbooks, peer-reviewed sources and prescribing guidelines. (Abbo et al., 2013; Dyar et al., 2014; Wasserman et al., 2017). The increasing sources of information available to students due to technological advancements can be a great tool to aid in teaching medical students about AMR, but sources should be verified and approved by educators to ensure that students get the correct information. In a South African study performed by Wasserman et al. (2017), knowledge scores were found to be higher in medical students who used prescribing guidelines, although the researchers found that the resources used to learn had no statistically significant bearing on the knowledge scores of students. In the same study - carried out by Wasserman et al., in 2017 on South African medical students - the majority of medical students felt inadequately prepared to prescribe antimicrobial medicines and were unsure about deciding factors such as whether to use combination therapy, the dosages and the duration of treatment when prescribing antimicrobial medicines. This was consistent with findings from the European and American studies, which also reported that the majority of students felt inadequately prepared to prescribe antimicrobial medicines. All the studies identified showed that medical students were open to learning more about AMR and

the prescribing of antimicrobial medicines. (Abbo et al., 2013; Dyar et al., 2014; Wasserman et al., 2017)

A review of 57 studies done worldwide by Mccullough et al. (2015) on prescribers' knowledge and beliefs on AMR showed that many prescribers believed that AMR was an important problem, and that antimicrobial medicines were overused. However, many believed that the overuse of antimicrobials occurred in healthcare settings other than their own, and many also blamed patients for non-adherence and overuse. This was consistent with the findings of a study carried out in South Africa, which showed that clinicians believed that AMR was a national problem, but tended to shift the blame for antimicrobial medicine overuse onto other healthcare professionals and patients (Farley et al., 2018). These findings were similar to the previously described studies carried out amongst medical students.

A recent study of doctors in Greece showed that they had adequate knowledge about antimicrobial prescribing and infectious disease management, but knowledge gaps still existed, such as knowledge about MRSA infections in the country (Spernovasilis et al., 2020). Another study done in Italy showed that although almost all the participants in the study were aware of AMR as a significant issue globally, there was little knowledge among doctors in Italy about multidrug resistant pathogens (Di Gennaro et al., 2020). These findings were consistent with the findings of a review by Mccullough et al. (2015), which found that there were inconsistencies and gaps in prescribers' knowledge about issues such as the prevalence of AMR in their practice settings. Farley et al. (2018) and Mccullough et al. (2015), found that higher knowledge levels among prescribers was associated with better prescribing practices. Those who were more knowledgeable were found to prescribe narrow spectrum antibiotics where possible. Another good practice that was associated with higher knowledge scores was delaying antimicrobial prescribing by informing patients of symptoms that should prompt seeking further medical attention and explaining the expected progression of disease. Prescribers who had incorrect perceptions, such as prescribing antimicrobials to patients where there was no need presented no harm to the patient were associated with lower knowledge scores (Farley et al., 2018; Mccullough et al., 2015).

The need to educate prescribers is evident from the findings of the studies by Farley et al. (2018) and Mccullough et al. (2015). In the research conducted by Farley et al. (2018) knowledge scores were related to age. The clinicians who were older than 55 years scored lower on knowledge tests than their younger counterparts. This may be attributed to an

improvement in AMR education at universities in the years since the older clinicians had completed their studies. However, many medical students expressed that they would benefit from more education on AMR. Farley et al (2018) suggested that education interventions should be implemented in both undergraduate and postgraduate education.

Similar to the medical students, prescribers in the worldwide study by Mccullough et al. (2015) and in the South African study by Farley et al. (2018) were receptive to learning more about antimicrobial medicines and AMR. Prescribers stated that they would benefit from better access to information on the resistance patterns in their locations, and more elaborate antimicrobial prescription guidelines. This presents an opportunity to educate prescribers and suggests that efforts to educate prescribers may yield positive results as it would be well-received. Prescribers were open to the use of electronic and internet based educational tools, which supports the idea that the use of technology in developing learning resources would be constructive. (Farley et al., 2018; Mccullough et al., 2015)

Education both in high income (HIC) and low- and middle- income countries (LMIC) should not only be focused on prescriber education, but also on educating the public on the correct use of antimicrobial medicines, and the consequences of misusing these medicines (WHO, 2015a, 2015b). Many prescribers stated that they felt pressure from patients to prescribe antimicrobial medicines even when there was no need for them (Farley et al., 2018; Mccullough et al., 2015). This correlates with the high proportion of prescribers who asked for more communication aids regarding AMR for more effective patient education. (Farley et al., 2018). Most AMS strategies that prescribers were aware of were focused on modifying prescriber behaviour, and few were aware of strategies to improve patient awareness (Mccullough et al., 2015). These strategies are important as effective AMS requires cooperation of both healthcare professionals and the public in the reduction of the misuse and overuse of antimicrobial medicines. (WHO, 2015a)

In studies carried out to evaluate perceptions, knowledge and practices among the public, it was reported that many people had heard of AMR – specifically about antibiotic resistance. (Carter et al., 2016; Mccullough et al., 2016). The majority of the public participants believed that the unnecessary use of antimicrobials and not completing an antibiotic course were major contributor to the rise of AMR. Although many people were aware that AMR existed, they had inadequate knowledge about it and about the correct use of antimicrobial medicines. A common belief was that resistance occurred from changes or immunity in the body resulting in antimicrobials being less effective (Carter et al., 2016; Mccullough et al., 2016). Another

common perception was that antibiotics were effective against viral infections such as colds, viral sore throat and flu (Carter et al., 2016; Khoury et al., 2018; Mccullough et al., 2016).

Regarding patient adherence to antimicrobial dosage regimens, participants in a Nigerian study conducted by Asekun-olarinmoye et al. (2014) reported that it was commonly believed that resistance was increased by not completing a course of antimicrobial medicines. Reasons provided for not completing a course included: stopping because of feeling better, not being able to afford to buy the full course of medication, or because of side effects. In a study done on Lebanese parents, some respondents reported that they felt that they could reduce the dose of antimicrobial medicines that their child was taking if the child was feeling better (Khoury et al., 2018). It is evident from these findings that there is a need for educational interventions aimed at the public to increase awareness of AMR. Effective communication with the public is imperative for these interventions to be effective.

In the studies that were reviewed, the most common sources of information about antimicrobial medicines among the public were the internet and media – specifically television and radio (Asekun-olarinmoye et al., 2014; Carter et al., 2016; Khoury et al., 2018). Some also reported receiving information from healthcare professionals. A knowledge of this could help governments and public health organisations design education interventions that appeal to the public and deliver them through channels that are most likely to reach a larger audience.

In a review carried out by McCullough et al. (2016) it was found that the public felt that resistance was due to the actions of others, which is similar to the results from healthcare professionals. The public also perceived a low personal risk from resistance. A contrasting finding was that the majority of the public reported that they trusted their clinicians' decisions regarding the use of antimicrobial medicines (Mccullough et al., 2016). This contrasted with the clinicians' belief that patients expected antimicrobial medicines. This supports the need for better communication between healthcare professionals and patients to avoid the unnecessary prescribing of antimicrobial medicines.

Objective 2: Strengthen the knowledge and evidence base through surveillance and research.

Understanding the patterns of antimicrobial resistance and prevalent infectious diseases can help prescribers make more appropriate decisions when selecting antimicrobial therapy for patients before diagnostic laboratory information becomes available (Felmingham, 2002). It is

difficult to predict the development and spread of resistant forms of microorganisms due to the complexity of such microorganisms and their adaptability to different biological and environmental conditions (Felmingham, 2002). Because of this, the incidence and mechanisms of resistance can vary between different geographical locations (Felmingham, 2002). It would therefore be helpful to prescribers if information such as local resistance patterns, characteristics of the pathogen in question and its antimicrobial susceptibilities were available. This would aid prescribers in making better prescribing decisions and more optimised empirical treatment plans for infectious diseases.

Incidence and prevalence patterns of infectious diseases are not well reported in many healthcare settings, especially in resource-limited countries. In South Africa, where there is a high burden of disease from infection, antimicrobial consumption data are scarce and obtaining them is challenging (Crowther-Gibson, et al., 2011). Having separate public and private healthcare sectors, coupled with economic constraints makes it more difficult to conduct studies to obtain such data (Schellack et al., 2017). Despite these challenges, South Africa is reported to have the most active AMR surveillance systems in Africa (Apalata et al., 2011). Different organisations run surveillance systems in the public and private sectors separately. These surveillance systems collect data from reliable and competent laboratories across South Africa and have been active for a number of years, which means that they have enough data to allow for determination of trends in AMR. (Schellack et al., 2017)

Both public and private sector AMR surveillance systems in South Africa have limitations. There is a lack of consistency in the data collection methods used by different institutions, which makes it challenging to make reasonable comparisons of the data obtained from different institutions or regions (Apalata et al., 2011). Current surveillance is also largely laboratory based, which places a focus on the organisms. Surveillance on infectious disease prevalence and antimicrobial consumption is also important. There is no differentiation between hospital-acquired and community-acquired infections, and it is impossible to determine the patient outcomes or the sites of infection from data obtained from these systems (Apalata et al., 2011).

Another limitation of the AMR surveillance systems in South Africa is a lack of representation for large proportions of the country. Private healthcare is affordable to only about 16% of the country's population (Schellack et al., 2017). The public sector surveillance system collects data mainly from the large academic hospitals in the country. Therefore, data collected from both public and private sectors are not representative of the whole country, as they do not

include information from smaller and rural healthcare facilities. (Crowther-Gibson, et al., 2011) Despite it not being representative, the information collected as a result of South Africa's surveillance systems is useful and according to Bamford et al. (2011, p 579) the country has "had a good start to AMR surveillance".

Reliable surveillance data provides information on local disease prevalence, but also sheds light on the effect of the consumption of antimicrobials and the development of AMR. According to Felmingham, (2002), comparable global surveillance programmes must collect data in a longitudinal fashion to allow them to identify resistance trends. They must be inclusive of data from other local, national, or international study sites. Resistance can spread rapidly between any geographical locations; therefore, it is important that surveillance studies do not focus on only one location. Such studies should not be influenced by corporate interests. It is therefore necessary that these programmes have quality assurance systems in place. In the case of South Africa, surveillance data from different laboratories where it is collected is conveyed to a co-ordinator who examines it and compiles a report on the data received. Such reports can be used to help prescribers make decisions based on local data and in the development of local antimicrobial prescribing guidelines.

Surveillance programmes must use standardised, well-defined and internationally recognised methods and protocols (Felmingham, 2002). It is also important to have a wide range of antimicrobials tested and must have quality control systems in place for all laboratory tests and data analysis. Clinical guidelines that direct patient care and the collection and handling of specimens need to be established. Clear guidelines for interpreting the surveillance data must be available (Felmingham, 2002). For the surveillance data to be useful to prescribers, they need to be able to understand them. It is best if the surveillance data are easily accessible to clinical staff in HICs and LMICs, for example using technology such as tablets and iPads. (Felmingham, 2002)

Effective surveillance systems require resources such as infrastructure, laboratory equipment and skilled personnel. This makes it difficult to carry out AMR surveillance in resource-limited settings such as in LMICs (Laxminarayan et al., 2013). Currently Sub-Saharan Africa, South and Southeast Asia have the least developed surveillance systems, and Europe and the Americas have the best surveillance coverage.

Objective 3: Reduce the incidence of infection through effective sanitation, hygiene, and infection prevention measures

With the rise in multi-drug resistant organisms comes the need for more antimicrobial medicines to be used to treat infections caused by these organisms. Putting measures in place to prevent the transmission of these pathogens is therefore an important step in AMS (Dik et al., 2016). The transmission of pathogens requires contact between a vehicle for the infection and a susceptible host (Whitelaw, 2015). Hospitals present a unique environment for infections as they house many vulnerable patients who are at a higher risk of contracting infections due to their pre-existing conditions. Patients may have compromised immune systems due to certain medical conditions or medications or may be vulnerable to infections due to invasive procedures such as surgery and invasive devices such as catheters and needles. Hospitals also experience high incidences of antimicrobial resistant organisms due to the high use of antimicrobials in these institutions. (Whitelaw, 2015)(WHO, 2015a)

Patients are constantly referred to different departments within hospitals depending on the type of care they require. This can cause transmission of infections from different areas of the hospital. Patients can also be referred to different hospitals and sometimes even to different cities. Considering that resistant pathogens are difficult to contain, infection control measures should not only be targeted within single hospitals but should be implemented throughout all hospitals for them to be effective (Ciccolini et al., 2013). These measures should not only be limited to large healthcare facilities with higher network connectivity but must also include smaller facilities such as smaller hospitals, clinics, private practices, and specialist care facilities. Efforts should also be made to collaborate regionally and across borders with infection control strategies to reduce the spread of infection (Ciccolini et al., 2013).

Miyawaki et al. (2010) found that in Japan integrating an infection control team at a hospital, combined with other interventions, resulted in lower average use of antimicrobials. This was despite an increase in admissions and surgical procedures. AMS is largely multifactorial and requires a combination of interventions used together strategically for it to be effective (Miyawaki et al., 2010). In the Netherlands, the success in the containment of MRSA is largely attributed to the collaboration between clinical microbiologists and infection prevention specialists. These groups work together to ensure the early detection and response to MRSA and other MDR infections and to develop infection control measures in hospitals such as hand washing guidelines (Köck et al., 2014).

Measures to prevent the transmission of infections to patients in hospital are therefore essential to any AMS programme (Ciccolini et al., 2013). Healthcare professionals come into contact with many different patients with different conditions, and it is therefore not uncommon for infections to spread through their hands. Hand hygiene is an important part of infection prevention and control. Disinfectants such as alcohol and chlorhexidine are widely used in healthcare facilities and are effective in preventing the transmission of infections (Whitelaw, 2015). Hand washing is inexpensive compared to other infection control measures and can be implemented in resource limited countries such as South Africa and Botswana.

Implementation of infection control measures may be challenging in resource-limited countries, such as in LMICs in Sub-Saharan Africa. Poor distribution of resources or lack of funds in these countries can lead to issues such as patient overcrowding, shortages of medicines and insufficient infrastructure and healthcare workers for infection control (Diaz et al., 2018). Healthcare workers are also put at a higher risk of contracting infections if proper precautions are not taken. (Newman, 2001) In developing countries where measures such as hand hygiene have been implemented in combination with other stewardship measures, there has been success in reducing the incidence of HAIs and therefore also reducing the need for antimicrobial medicines (Murni et al., 2015).

Objective 4: Optimize the use of antimicrobial medicines in human and animal health

AMR is driven by the use of antimicrobial medicines, and the overuse and misuse of the medicines exacerbates the problem. Effective AMS is multifactorial and requires many elements to work together within healthcare systems and other sectors. Factors that cause the misuse of antimicrobials include poor prescribing practices, ease of access to antimicrobials, poor adherence, lack of AMS guidelines and poor practices in agriculture and animal health. (WHO, 2015a) In healthcare, guidelines need to be put in place to direct the prescribing decisions of healthcare professionals for optimal use of antimicrobials. The Worldwide Country Situational Analysis on the Response to Antimicrobial Resistance (2018) found that many countries had no guidelines in place for the proper prescribing of antimicrobial medicines. In the places where guidelines did exist, they were difficult to enforce because of the ease of access to antimicrobials without prescription. (WHO, 2015b)

For AMS to be successful, access to antimicrobials should be controlled and limited to healthcare professionals who are trained to prescribe and dispense these medications. (Tarrant et al., 2019) In LMICs, access to antimicrobial medicines is difficult to control as in many areas

these medicines are available without a doctor's prescription (WHO, 2015b). This causes increased rates of self-medication with these medicines for conditions that may be self-limiting or incorrect use of the medicines, for example, the use of antibiotics to treat symptoms such as sore throat and cough. In settings where the use of antimicrobials are controlled by prescribers, the responsibility to make prescribing decisions is often placed on junior staff with little experience and training. (Tarrant et al., 2019) LMICs are also burdened with high amounts of counterfeit antimicrobial medicines, which make it more challenging to control the use of antimicrobials and the incidence of AMR. (WHO, 2015b)

In many settings antimicrobial medicines are prescribed by doctors, hence they are usually the targets of interventions aimed at optimising the use of antimicrobials in human medicine. (Tarrant et al., 2019) A study done in Europe found that although GPs were aware of the development of AMR and the effects of unnecessary antimicrobial prescribing, they still faced challenges following their antimicrobial prescribing guidelines (O'Doherty et al., 2019). According to the GPs, the guidelines did not provide clear outlines and instructions to cater for situations where many variables occurred. They felt that factors such as the uniqueness of a patient's condition, other pre-existing conditions and the general health of the patient needed to be considered when making the decision to prescribe an antimicrobial medicine and were not addressed in their guidelines. This made it difficult for them to follow the guidelines in their daily practice. (O'Doherty et al., 2019)

General Practitioners in Europe also expressed that they felt pressure from patients to prescribe antimicrobials. A financial and ethical dilemma was evident, where GPs reported trying to satisfy patients' expectations for antimicrobial medicines even when they felt the patients may not have needed them in order to retain those patients to their practice. It was reported that patients who did not receive free healthcare and had to pay for their GP consultations had a higher expectation for antimicrobials, and the pressure to maintain a good relationship with such patients was high among GPs. Patients' expectations of antimicrobials could possibly be attributed to past experiences, where they would have received antimicrobials for conditions such as respiratory tract infections so they would continue to expect the same treatment. (O'Doherty et al., 2019)

Respiratory medicine is important in AMS due to the high rates of inappropriate antibiotic prescriptions for viral respiratory tract infections compared to other infections (Broom et al., 2017). This drives the development of resistant strains of bacteria to commonly used

antibiotics. AMS strategies need to be implemented in respiratory medicine to reduce the spread of resistance. However, barriers to the effective functioning of these strategies, such as poor inter-professional relationships and cultural and behavioural aspects were found to be among the factors that influence AMS (Broom et al., 2017). Broom et al (2017) found that some physicians were resistant to accepting the input from AMS services, and conflict arose when prescribers and members of the AMS services had conflicting opinions on the selection of antimicrobial medicines. They also found that nursing staff were inadequately trained in the aspects of AMS.

A study carried out in two Australian hospitals found that the AMS systems that were in place resulted in some conflict between staff of different specialties. These hospitals used an approval system, where prescriptions for antimicrobial medicines had to be approved by an AMS doctor first, who would be an infection control specialist. The majority of the respiratory physicians were not receptive to advice from infection control specialists and considered any unsolicited advice to be invasive to their clinical territory. AMS systems were reported to upset the hierarchies in place as it was viewed to be insulting by some of the senior physicians when the approving AMS doctor was a junior. According to the respiratory physicians, the approval system also caused confusion among some junior staff in cases where the AMS advice provided contradicted the respiratory physician's prescribing decision. (Broom et al., 2017)

Another barrier to these AMS systems that the nursing staff in the Australian hospitals felt was that administering the prescribed medicine in a timely manner was more important than waiting for approval in instances where approval was delayed. Nurses felt that they had an obligation to their patients to prevent adverse therapeutic outcomes, and to also protect themselves from reputational damage and legal implications of not administering the medications prescribed (Broom et al., 2017). Physicians also have a moral and ethical obligation to act in the best interest of their patients to achieve positive clinical outcomes (General Medical Council, 2021). This creates a conflict for physicians as they are inclined to prioritise the health and wellbeing of their patients over the interests of society (Broom et al., 2017).

Objective 5: Develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions

The surge in the development of AMR means that existing antimicrobial medicines are losing efficacy in treating infectious diseases (van Hengel & Marin, 2019). There is a need for the

development of more cost-effective diagnostic tools to reduce the rate of empirical prescribing of antimicrobials, as most diagnostic tools on the market remain expensive, and LMICs are the most affected by this. The need for investment in the development of new antimicrobial medicines, diagnostic tools and vaccines is therefore increasing. Fears that antimicrobial medicines may lose their efficacy rapidly due to AMR and the increased control of the use of these medicines will result in lower profits have deterred pharmaceutical companies from investing in their research, innovation and development (WHO, 2015a).

The economic impact of non-action towards the growing problem of AMR needs to be evaluated. According to a report by the World Bank, the economic impact of AMR could result in significant losses of between 1.1% to 3.8% in the world's annual gross domestic product (GDP) by 2050 (Jonas et al., 2017). Low income countries are expected to be highly affected, with projected losses of over 5% of GDP in 2050 and beyond (Jonas et al., 2017). The majority of people who will be affected by this would be those living in low income countries (Jonas et al., 2017). Because AMR cannot be confined by borders, its effects are not limited to low-income countries only, but are in fact, global.

Research and innovation in important novel solutions and tools to address issues that perpetuate the development of AMR are needed. Progress in these areas can only be sustainable if policies which support the work of researchers are put in place. The relationship between policy makers and researchers has to be mutually beneficial as the research carried out has to enlighten and strengthen policy making. In the European Union (EU), the support of the Joint Programming Initiative on AMR (JPIAMR) allowed for the collaboration between 27 countries in that region in their national research projects (van Hengel & Marin, 2019). Collaboration between private and public partners also has a positive impact on researchers. The collaboration between the European Commission and its industry partners made more funding available to researchers, and in turn their research could aid policy makers in their work. (van Hengel & Marin, 2019)

2.4.2 Antimicrobial stewardship in hospital settings

2.4.2.1 Approach to antimicrobial therapy

Clinical diagnosis is guided by a combination of several factors. The process of diagnosing usually begins with a clinical examination to determine the presenting signs and symptoms, and history taking to determine possible infective pathogen. The site of infection should be identified as it is an important consideration which may affect the drug's ability to enter the

site and produce the desired results (Hooper et al., 2015). Host factors such as age, pre-existing conditions, other medical therapy, and allergies should also be determined (Leekha et al., 2011). Local resistance profiles and/or exposure history may also be useful in diagnosing the patient's condition (Hooper et al., 2015). National and local formulary restrictions and shortages determine the medicines available for prescription and administration to the patient (Hooper et al., 2015).

Before initiation of antimicrobial therapy, an infectious disease diagnosis must be made. The initial diagnosis is often a tentative diagnosis made before laboratory test results such as microscopy, culture, and sensitivity (MC&S) results are available (Leekha et al., 2011). Antimicrobial therapy can be initiated based on this diagnosis and adjusted as laboratory results become available. This is known as empirical treatment (Hooper et al., 2015). A microbiological diagnosis should be obtained where possible. When this happens, the pathogen can be identified, and it can be tested to determine what antimicrobials it is susceptible to (Leekha et al., 2011). Antimicrobial therapy can then be initiated based on this information. This is called directed therapy (Hooper et al., 2015).

2.4.2.1.1 Microbiological diagnosis

Some infectious diseases are sufficiently unique in their clinical presentation to be recognised from the signs and symptoms alone, or to determine the most likely causative agent. For example, in patients presenting with cellulitis, the causative agent is usually assumed to be streptococci or staphylococci, and antimicrobial medicines may be prescribed based on this assumption (Leekha et al., 2011).

However, most infectious diseases are not characteristically unique. Most pathogens can cause a wide range of symptoms that vary between patients, and a single clinical symptom can be caused by a wide range of pathogens, which makes it impossible to determine the causative agent without the help of microbiological diagnosis (Hooper et al., 2015).

Microbiological diagnosis refers to the laboratory examination of microbiological specimens collected from the patient to determine the causative agent of a disease. The selection of the specimens to be collected is based on the findings of the clinical examination. Where possible, the specimens should be collected for microbiological testing before the initiation of empirical antimicrobial therapy. Once they are available, the microbiological test results can be used to adjust the antimicrobial therapy to directed therapy (Leekha et al., 2011).

Specimens for microbiological examinations may be collected in various ways. It is important to prevent contamination of specimens as much as possible. Swabs are a common means of collecting specimens and may be used to collect specimens from the skin and mucous membranes. However, swabs are usually not optimal due to low yield of microbiological materials (Washington, 1996). Other examples of specimens that may be collected include sputum, transtracheal aspirate, bronchoalveolar lavage fluid, gastric aspirate, urine, stool, tissue, lymph nodes, cerebrospinal fluid, and blood (Riedel et al., 2019b).

Microorganisms present in specimens may be identified using several different techniques. Specimens may be directly examined under a microscope using various processes such as Giemsa staining and Gram staining which allow for rapid diagnosis (Washington, 1996). Cell morphology can be studied under a microscope to determine the microorganism present. For example, the presence of a thick peptidoglycan layer with no outer membrane indicates Gram-positive bacteria, while a thin peptidoglycan layer with a cell membrane present indicates the presence of Gram-negative bacteria (Actor, 2012). In some instances, the culturing of microorganisms is required for a diagnosis to be made. Cultures are grown either in liquid broth or solid agar (Actor, 2012). Antimicrobial agents can also be added to the culture medium to make it selective for certain microorganisms (Washington, 1996). In some instances, viruses are inoculated into live animals such as mice or guinea pigs to isolate them (Washington, 1996).

For microorganisms that cannot be isolated using culture methods, serodiagnosis may be useful in identification. Blood specimens from the patient are analysed for the presence of certain antibodies such as the IgM and IgG antibodies that are created as part of the immune response towards colonisation by certain pathogens (Neocleous et al., 2013). The hepatitis, Epstein-Barr and HIV-1 viruses may all be diagnosed in this way (Washington, 1996). However, the drawbacks of serological diagnosis are that the results obtained may not be representative of the patient's condition. It takes time for the body to elicit an immune response from the time of infection, therefore samples may be taken before the antibodies are produced (Neocleous et al., 2013). Immunocompromised patients may not be able to elicit an immune response at all, or may have a delayed response (Neocleous et al., 2013). Furthermore, the test may detect antibodies from a previous infection (Neocleous et al., 2013).

Microbiological testing is also used to analyse the microorganism's susceptibility to different antimicrobial medicines. The microorganisms are exposed to different antimicrobial agents in vitro through processes such as disk diffusion (Washington, 1996). Susceptibility testing helps

to narrow down antimicrobial therapy to the specific needs of the patient and is one of the key factors in reducing antimicrobial resistance through antimicrobial stewardship (Dellit, 2007).

2.4.2.1.2 Directed/definitive and empirical therapy

The prescribers' choice of antimicrobial may be based on a confirmed diagnosis of a specific pathogen through microbiological testing. This is called directed or definitive therapy. This usually allows for the selection of narrow spectrum medicines according to the organism's susceptibility profile and the extent and severity of the infection (Leekha et al., 2011). This type of therapy can reduce the occurrence of undesired effects such as the development of AMR (Dellit, 2007).

Although microbiological testing allows for more targeted therapy, the results of these tests can take between 24 and 72 hours to become available, and in resource-limited settings this time might be even longer (Leekha et al., 2011). In critically ill patients, the timely administration of antimicrobials is crucial. For example, delayed antimicrobial therapy in patients infected with *Staphylococcus aureus* bacteria has been associated with poor patient outcomes (Lodise et al., 2003). In many cases, prescribers make a diagnosis and prescribe antimicrobial medicines based on the symptoms and severity of the illness, epidemiological information and patient's past conditions and exposure (Hooper et al., 2015; Leekha et al., 2011). This is called empirical therapy. This type of therapy usually involves the prescription of broad-spectrum antimicrobials, or a combination of antimicrobials, to cover a wider range of pathogens (Hooper et al., 2015).

Where empirical therapy is used, it is still important to obtain specimens for laboratory testing before the initiation of the antimicrobial therapy (Leekha et al., 2011). This will allow for the de-escalation of treatment to the point of directed therapy once more information on the causative agent is available (Hooper et al., 2015).

2.4.2.1.3 Prophylaxis

In some instances, the prescription of antimicrobial medicines for prophylaxis may be appropriate. For patients undergoing surgery, prophylaxis against postoperative surgical site infections may be appropriate. In patients undergoing implantation surgery or surgical procedures known to have high infection rates, and those in which the consequences are high if an infection is acquired prophylaxis is required (Hooper et al., 2015). The spectrum of activity of the antimicrobial used should always be specific to the microorganisms usually associated with surgical site infections (Anandalwar et al., 2020).

2.4.2.1.4 Site of infection

Effective antimicrobial therapy is dependent on the medicine's ability to reach therapeutic concentrations at the site of infection. Certain sites of infection may be more difficult for medicines to reach than others. Normal host defences like the blood-brain barrier, abscess cavities, and immunological functions may affect the efficacy of antimicrobial medicines (Onufrak et al., 2016). This may be improved by: combining medicines to improve permeability to the site, using a different route of administration, or using procedures like drainage or debridement to remove or reduce the barriers to medicine penetration (Hooper et al., 2015). For example: to treat meningitis, the antimicrobial medicine needs to penetrate the blood-brain barrier to reach therapeutic concentrations in the cerebrospinal fluid (Onufrak et al., 2016). Penetration of the blood-brain barrier may be improved by adding agents such as dexamethasone or rifampicin, which may improve penetration for certain antimicrobials (Nau et al., 2010). For example, rifampicin may be used as an adjunct to improve CSF penetration of ceftriaxone in the treatment of meningitis (Nau et al., 2010).

In osteomyelitis, the spectrum of activity of the antimicrobial is important. However, susceptibility tests are usually conducted using serum drug concentrations and these may differ greatly from concentrations achievable in the bone (Fraimow, 2009). Measurements of concentrations of cephalosporins done in healthy bone tissue showed only 10-20% of the serum concentrations achieved by the same drugs (Fraimow, 2009). In infected bone tissue, penetration of the antimicrobial into the tissue may be even lower due to normal host defences, the presence of biofilms which the antimicrobial has to penetrate and the alteration of factors such as pH that result from the presence of bacteria (Fraimow, 2009).

For the treatment of prostatitis, the antimicrobial must reach therapeutic concentrations in prostate secretion and tissue. Fluoroquinolones may be used as they are able to penetrate the prostate and reach therapeutic concentrations after oral administration (Magri et al., 2018). Direct injection into the prostate may also be considered as it would introduce the antimicrobial directly to the site of infection (Magri et al., 2018).

Other sites where therapeutic drug concentrations may be difficult to reach include intraocular fluid and abscess cavities (Leekha et al., 2011).

2.4.2.1.5 Allergies

Patient's allergy history should be considered to help select the appropriate antimicrobial therapy. Allergies to antimicrobials are common, with penicillin allergies being the most common in this category (Hooper et al., 2015).

2.4.2.1.6 Drug-drug interactions

Antimicrobial medicines may interact with other medicines given to patients. A comprehensive patient history should report any medications that the patient may have taken prior to antimicrobial initiation, and medicines that the patient may have to take concurrently with the antimicrobial therapy. Medicine reconciliation is a strategy that involves comparing a list of the patient's current medications to a list of the proposed medications to be prescribed and determining the best treatment option for that patient (Weber, 2020). This is also done when patients are discharged with medicines to determine whether there might be adverse interactions with any medications they might be taking at home (Weber, 2020). This can be used to improve patient safety and prevent adverse drug-drug interactions. Medicine reconciliation is one of the important functions performed by pharmacists.

Antimicrobial stewardship measures can be adopted in hospitals to monitor and guide the use of antimicrobial medicines in these settings to promote optimal antimicrobial use and reduced the incidence of adverse events in patients and AMR.

2.4.2.2 Hospital antimicrobial stewardship programmes (ASPs)

Having a dedicated programme for the monitoring of antimicrobial medicines can help to improve antimicrobial utilisation practices in hospitals. The CDC outlines the essential elements for implementing effective hospital ASPs (CDC, 2019). To improve the use of antimicrobial medicines, the areas of antimicrobial prescribing that require improving should be identified, and then the strategies to address them defined and implemented (CDC, 2019). AMS strategies that can be used include: prospective audit and feedback, preauthorisation of antimicrobials, the development of AMS guidelines and the education of healthcare professionals on AMS.

2.4.2.2.1 Strategies to improve antimicrobial prescribing

Prospective audit and feedback are an intervention that can be implemented to improve antimicrobial prescribing in a hospital setting. This is one of the strategies that is recommended by the IDSA as it has been effective in improving antimicrobial prescribing practices in hospital

settings (Høgli et al., 2016). In prospective audit and feedback, the professional practices of healthcare professionals are measured and evaluated against the defined standards of professional practice. The results of this evaluation are then reported back to the healthcare professionals (Ivers et al., 2012). In a study reviewing AMS interventions used in South African hospitals, audit and feedback was one of the interventions that were implemented in South African hospitals (Chetty et al., 2019). This intervention can be implemented in combination with other AMS strategies to help improve antimicrobial prescribing practices. Chetty et al. (2019) emphasised the importance of implementing audit and feedback in collaboration with other AMS interventions in hospitals to improve antimicrobial prescribing practices.

Preauthorization is another intervention that is recommended by the CDC. Using this intervention, prescribers are required to obtain approval before prescribing certain antimicrobial medicines. This strategy can be used to control the use of certain antimicrobials to reduce exposure and limit the chances of the development of AMR in these pathogens (CDC, 2019). Local resistance information and expertise of the members of the AMS committee should be used to determine which antimicrobials require preauthorisation and close monitoring (CDC, 2019).

AMS guidelines also recommend the development of antimicrobial prescribing guidelines that are facility specific (CDC, 2019; WHO, 2015a). These guidelines should be based on evidence-based national and international antimicrobial prescribing guidelines. The use of facility specific guidelines can help to optimise the selection of antimicrobial therapy based on local trends such as local resistance and susceptibility patterns and local disease incidence (CDC, 2019). These guidelines should be made available to prescribers to guide their prescribing decisions.

Education of healthcare professionals and the public is important in improving the use of antimicrobials. According to Chetty et al. (2019), education interventions are a significant part of ASPs and are essential to the success of ASPs. Educational interventions can include updating prescribers on new developments in antimicrobial therapy or strengthening the knowledge of existing guidelines and interventions. This can be implemented in formal educational sessions or informal means such as posters flyers (CDC, 2019).

2.4.2.2.2 Hospital AMS committee

Guidelines for AMS recommend a multidisciplinary AMS committee to be responsible for ASPs in hospitals (Dellit et al., 2007). According to the IDSA and SHEA AMS guidelines, the

AMS committee should be led by an infectious disease physician, and they also recommend co-leadership with a pharmacist (Dellit et al., 2007). This pharmacist should have infectious disease expertise. The membership of the AMS committee should also include a clinical microbiologist, information systems specialist, infection control professional, and a hospital epidemiologist (Dellit et al., 2007). The guidelines emphasise the importance of bringing together infection control, pharmacy, and the therapeutics committee for the implementation of hospital ASPs.

The CDC has outlined the essential elements that are essential when implementing hospital ASPs. For AMS in hospitals to be successful, the input and support of hospital management is essential (CDC, 2019; Dellit et al., 2007). Hospital management needs to ensure that the ASPs are adequately provided with staff, time and other resources needed to support the programme. To determine the exact resources needed, communication between the leaders of the AMS committee and hospital management is important (CDC, 2019). Hospital management plays an essential role in integrating AMS into other activities and initiatives in the hospital and ensuring that other departments are informed about ASPs. Management should have defined roles and responsibilities for the AMS committee (CDC, 2019). The AMS committee should report back to management on matters relating to AMS in the hospital (CDC, 2019).

2.4.3 Antimicrobial Stewardship in Botswana

There have been limited studies on the utilisation of antimicrobial medicines in Botswana. In a study conducted in PHC facilities in Botswana, prescribing practices were found to be good as evidenced by the high percentage of prescriptions that were in accordance with the Botswana Essential Drug List (EDL) and that were prescribed by their International Non-proprietary Name (INN), which were used in the study as measures of good prescribing practices (Mashalla et al., 2017). For the antibiotic prescriptions that were deemed to be unnecessary, insufficient training, socio-cultural factors and demand from patients were cited as the reasons for this occurring.

A concern in Botswana is the high prevalence of HIV infection, which according to Paramadhas et al. (2019) may drive up the empiric antimicrobial prescribing in infected patients. Another concern is the high use of IV antimicrobials without de-escalating to oral antimicrobials (Paramadhas et al., 2019). According to a report on a meeting held to discuss ongoing initiatives to improve antimicrobial use in Botswana, high parenteral antimicrobial

use, the lack of ASPs and antimicrobial prescribing guidelines in hospitals were among the issues that were being addressed in Botswana (Tiroyakgosi et al., 2018).

Measures are being taken in Botswana to improve the utilisation of antimicrobial medicines. These include collaboration with groups such as the Medicines Utilization Research in Africa (MURIA) group to educate healthcare professionals on the rational use of antimicrobial medicines (Massele et al., 2015). Some of the initiatives that are being explored in Botswana include conducting more drug utilisation studies to better determine what interventions are needed to reduce AMR, and collaborating with other African countries to promote drug development and the rational use of medicines across the continent (Massele et al., 2015).

This concludes the literature review chapter. The following chapter describes the methods used when conducting this study.

Chapter 3: Methodology

This chapter provides detailed information about the methodology used in this research study. It provides information about the study design, the study site, the sample, and the sample size. It also describes how quantitative and qualitative data was collected and analysed.

3.1 Study Design

This study was guided by a positivist paradigm. Creswell (2009) defines the positivist paradigm as an approach to research enquiry that relies on scientific evidence about human experiences. The research was a cross-sectional, descriptive, mixed methods and observational design to determine the antimicrobial prescribing practices at Mahalapye District Hospital (MDH). Data collection was carried out by the primary researcher at MDH for a period of approximately 3 months from the 7th of January to the 3rd of April 2019.

3.2 Study Site

This study was carried out in Mahalapye, a town located in the Central District of Botswana. The Central District is divided into sub-districts and Mahalapye is located in the Central Mahalapye sub-district, of which it is the capital. Mahalapye is located just north of the Tropic of Capricorn, about 200km north-east of the capital, Gaborone, and almost halfway between the two largest cities in the country. The Central Mahalapye sub-district has a population of approximately 118 875 (Statistics Botswana, 2015). Mahalapye makes up approximately 46 000 (39%) of this population (Statistics Botswana, 2015).

The MDH was officially opened in 2008 as part of efforts by the government of Botswana to improve access to healthcare and specialist services in different parts of the country. It was one of four hospitals that were built as part of these efforts (Merafhe, 2008). MDH is a multifunctional facility, providing both primary and secondary care (Tshitenge et al., 2016). The hospital has 260 beds and caters for both adult and paediatric patients (Merafhe, 2008). Patients younger than 14 are admitted to the paediatric medical ward after being screened at the Accident and Emergency department. The staff in the paediatric ward included medical doctors and registered nurses. At the time of the study, there was no paediatrician at the hospital, and no dedicated ward pharmacist for the paediatric medical ward. Patients at MDH

include patients who have been referred from other hospitals and clinics in surrounding areas and patients who go to MDH as their first point of care.

3.3 Study Sample

This study has a quantitative and a qualitative aspect to it. Paediatric patient files were analysed quantitatively, and healthcare workers at MDH were interviewed. The data from the interviews was analysed qualitatively.

3.3.1 Selection of the study sample

The study aimed to collect patient data retrospectively for a period of 12 months. The patient data collection commenced in January 2019, and the data collected were from January 2018 to December 2018. The data collected was retrospective and provided the most recent account of the prescribing practices at this hospital at the time of the study.

The inclusion criteria were: Files with prescriptions of patients in the paediatric medical ward with at least one antimicrobial prescribed.

Prescriptions with incomplete information (e.g., weight or HIV status) were included and the absence of information was recorded as part of the findings of the study.

Files with no antimicrobials prescribed during the selected time period were excluded from the study.

For qualitative data collection, a purposive sampling method was used. Participants for the semi-structured interviews were selected according to their roles and responsibilities at MDH. Participants had to be employed at MDH, speak English and be directly responsible for prescribing, dispensing, or administering medication to patients admitted to the paediatric medical ward.

3.3.2 Sample Size considerations

Before the study was carried out, information was obtained telephonically from the records department of the hospital regarding the number of patients who were admitted to the paediatric medical ward every month. From this information, it was estimated that there were approximately 230 in-patients in the paediatric medical ward at MDH for the period between July 2018 and December 2018. This number was doubled for January 2018 to December 2018

i.e., 460, and represents the population size (N) in the following equation used to calculate sample size.

$$n = \frac{z^2 \times p(1-p)}{e^2}$$

Where: n= sample size; e= margin of error; z= confidence level score or z-score; N= population size; p= population proportion. (Smith, 2013)

3.3.2.1 Margin of error (e)

When a study is conducted the possibility of errors occurring must be acknowledged and accounted for. The margin of error is the value we are willing to accept as the error in the estimate obtained. Larger sample sizes will result in smaller sampling errors. Values between 2-5% are usually accepted. (Martínez-Mesa et al., 2014) For this calculation, a 5% margin of error was used.

3.3.2.2 Confidence level (z)

A confidence level is the probability that all the samples can be expected to include the true population parameter, which means that they will be within the estimated margin of error. For example, if a study allows for a 5% margin of error, that means that the researcher can be 95% certain that if the study were to be repeated the same results would be obtained. The Z-value is the statistic corresponding to the confidence level. For a 90% confidence level, the Z-value is 1.645, and this is what we used for this study. (Smith, 2013)

3.3.2.3 Population proportion (p)

The population proportion or standard deviation denotes the extent to which the sample will deviate from the population mean. Since the population size is unknown, a population proportion of 0.5 is used as the maximum extent to which the sample can deviate from the mean in 50%. (Smith, 2013)

$$n = \frac{(1.645)^2 \times 0.5(1-0.5)}{(0.05)^2}$$

$$= 270$$

This representative sample of 270 was used to guide the selection of patient files.

3.4 Collection of patient information

The patient register, which contained a list of patients who had been admitted to the paediatric medical ward each month, was used to select the patient files to be used for the study. The register included the patient hospital number and diagnoses. Patient files were selected according to the patients' diagnoses. If antimicrobial therapy was indicated for the treatment of the condition diagnosed, then that file was selected. Files were also selected if antimicrobials were commonly used for prophylaxis in the conditions diagnosed. A list of the patient hospital numbers on the files was submitted in a formal request to the hospital's Records Department who were responsible for locating and providing the files requested to the researcher. As part of their security measures, the Records Department permitted the researcher to extract data from the files in a secure location of the hospital for a maximum of three days before the files had to be returned. Because of this, files were requested, and data was collected chronologically (from month to month) according to the patient register.

Data was collected from patient files using the Antibiotic Prescription Chart, which was created as part of the South African Antimicrobial Stewardship Programme (SAASP) (Appendix A) (Boyles et al. 2013). Permission to use the chart was granted by the author (Appendix B). The Antibiotic Prescription Chart is a data collection tool designed for use in analysing antimicrobial prescribing and use. The prescription chart was modified slightly by the researcher to include capacity to record the sex and age of the patient. This modified version of the Antibiotic Prescription Chart was used to collect information about the patients without collecting any of the patients' identifiable information such as names or addresses. The prescription tool at MDH was a generic prescription chart used for all medication prescriptions, not specific to antimicrobial medicines. The following information was collected from each patient file according to the modified Antibiotic Prescription Chart:

- Age
- Sex
- Weight
- Allergy information
- HIV status

- Diagnosis
- Source of infection
- Antimicrobial medication prescribed
- Indication of antimicrobial treatment
- Dosages prescribed
- Duration of treatment
- Cultures sent to the laboratory for analysis and the results

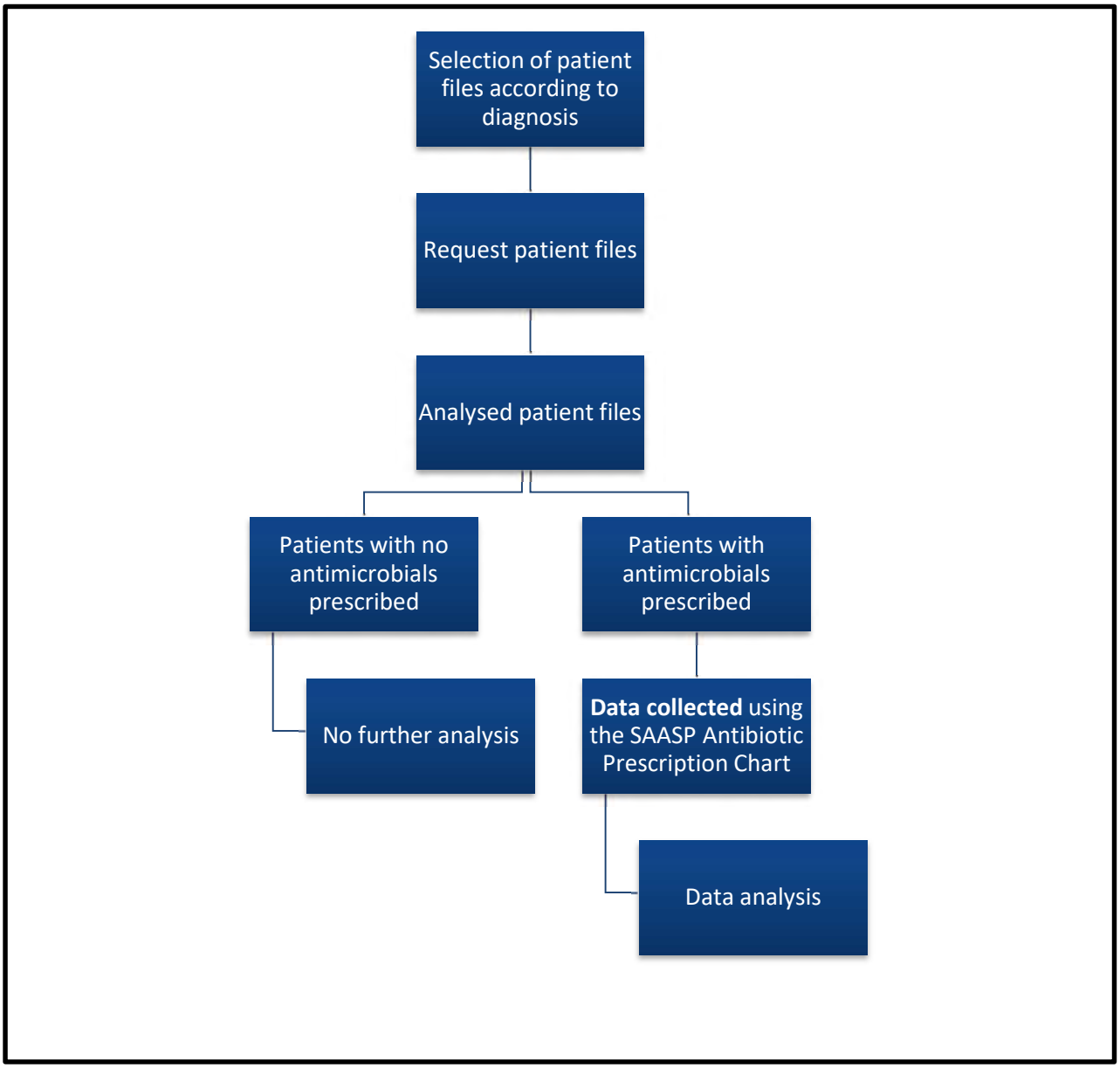


Figure 3.1: Flow diagram of the data collection process

3.5 Semi-structured interviews

This research was conducted to evaluate the antimicrobial prescribing practices in paediatric patients at MDH. Various qualitative research methods were considered. Questionnaires were considered as a data collection tool as they would allow the researcher to present questions to participants and allow them to respond in their spare time. However, these would not allow the researcher to redirect certain questions in real time. Focus group discussions were also not an ideal data collection method as it was difficult to coordinate times for different healthcare professionals with different roles and responsibilities to participate at the same time and could possibly interfere with their duties. Face-to-face semi-structured interviews were selected as the data collection method as these allowed the researcher to redirect the questions where necessary.

Semi-structured interviews are a common method used to collect data in qualitative research studies in primary healthcare settings (Kallio et al., 2016). The advantages of using this method include that it is flexible and allows the researcher to probe deeper and gain a better understanding of a participant's thoughts and opinions on a particular topic, and also allows for the collection of open-ended data (Kallio et al., 2016). With semi-structured interviews, researchers are able to collect meaningful data and conduct feasible studies even with a few participants (DeJonckheere & Vaughn, 2019). Where a mixed methods approach is used in research, information obtained from semi-structured interviews may be used to explain the results from the quantitative portion of the study (DeJonckheere & Vaughn, 2019).

These interviews were voluntary. Staff involved in the prescribing and dispensing of antimicrobials in the paediatric ward were invited to be interviewed to obtain information about the policies and programs regarding the prescribing and use of antimicrobials in the hospital. Members of staff in the paediatric ward were introduced to the researcher, who explained the purpose of the study and what the interviews would entail. They were given the opportunity to agree or decline to be interviewed as part of this research study. Potential participants were given a printed copy of the Interviewee Information (Appendix C) and a consent form (Appendix D) at least 24 hours before the interview was scheduled. At the beginning of each interview, the researcher read through and asked if the participants understood the information provided to them. Participants were also given the opportunity to ask questions or express concerns about the study before the interview commenced. Once the researcher had ascertained

that the interviewees understood were satisfied with the information provided to them, participants were asked to sign the informed consent form, and the interview would begin.

Interviews were conducted with different members of staff. All the interviews were conducted face to face with each participant separately at MDH. The first interview was conducted with a medical officer in the paediatric ward on the 28th of March 2019. At the time of this study there was no paediatrician at this hospital. The second interview was conducted with one of the nursing staff in the paediatric ward on the 28th of March 2019. The third interview was conducted on the 3rd of April 2019 with one of the pharmacists at the hospital, who was also part of the committee involved in establishing an Antimicrobial Stewardship Committee at MDH. For each interview, a quiet space such as an empty office or break room within the hospital was utilised which offered an appropriate environment for the interviews to be conducted.

The interviewees were asked questions guided by the approved interview guide (Appendix E). The questions were designed to gather information about the AMS measures in place at MDH, as well as the interviewees' opinions and perceptions of AMS. If the interviewees did not understand the questions asked, the interviewee explained the question in different words to aid in understanding without changing the question. The interviews were recorded electronically using a voice recorder. The interviews were transcribed verbatim in a text document in Microsoft Word® (2010) (Microsoft Corp, Redmond, WA, USA).

3.6 Particulars of data collected during the study

3.6.1 Patient information

The information obtained from the patient files was transferred into a spread sheet in Microsoft Excel® (2010) (Microsoft Corp, Redmond, WA, USA) so that statistical analyses could be performed. Descriptive statistics were used to summarize the data. Frequencies and percentages were used for categorical data.

The data were analysed according to:

- Duration of treatment
- Concurrent use of antimicrobials
- Indication of treatment

- Prescription guidelines
- HIV Status

These were defined as follows:

Duration of treatment

The number of days of antimicrobial treatment were calculated and grouped into four categories, namely, less than 5 days, 5 to 7 days, 8 to 10 days and longer than 10 days (Johnston et al., 2018). Antimicrobials which were prescribed and not administered to the patient were also recorded and grouped as "not given" in a fifth category.

Concurrent use of antimicrobials

Where two or more antimicrobials were administered at the same time, this was defined as concurrent use (Johnston et al., 2018). This definition included situations where two or more antimicrobials were initiated at the same time, or where at least one antimicrobial was added to a treatment regimen which previously consisted of one antimicrobial.

Indication of treatment

Indication of treatment was categorised as empiric, definitive, or prophylactic (Johnston et al., 2018). Indication was defined as empiric when treatment was initiated with no culture results available. Antimicrobial treatment that was initiated after a culture result indicating sensitivity to that antimicrobial was defined as definitive. Antimicrobial treatment that was initiated with no diagnosis of an infectious disease was defined as prophylactic. Where antimicrobial treatment was initiated empirically, but during the course of treatment culture results were obtained and treatment was continued or changed depending on sensitivity results. (Johnston et al., 2018)

Adherence to prescribing guidelines

The prescribed antimicrobial treatment was compared to the guidelines stipulated in the Botswana Antimicrobial Therapy Guide (Botswana Ministry of Health, 2012) to analyse compliance. These guidelines were produced by the National Standing Committee on Drugs, which is part of the Ministry of Health in Botswana and are aimed at providing healthcare professionals with evidence-based recommendations for the treatment and management of

infectious diseases commonly seen in Botswana. These guidelines were provided by the head of the pharmacy department at MDH as the guidelines that are used at this hospital.

The guidelines were comprised of twelve chapters. The second chapter contained a list of antimicrobial medicines and information including their spectrums of activity, therapeutic uses and recommended doses for adults and children. Chapters three to twelve contained details of different infectious conditions and indications for antimicrobial therapy. The information in these chapters included the recommended antimicrobial therapy for those conditions and also alternative therapy recommended. For this study, adherence to antimicrobial guidelines was measured by selection of the antimicrobial medicine. Dose and duration of the antimicrobial medicines prescribed was measured, however these parameters were not used to determine adherence as this was a retrospective study, therefore dose adjustments made based on the patient's condition would have been difficult to account for.

To determine adherence to antimicrobial therapy, the researcher first looked at the diagnosis and then compared the antimicrobial therapy prescribed to the recommended treatment options for that condition in chapter three to twelve of the guidelines. If the antimicrobials prescribed were the same as those recommended by the guidelines, then the prescription was deemed to be adherent. If the prescription was not the same as the recommended treatment, it would then be compared to the alternative treatment recommendations under the same indication. If the antimicrobials prescribed were in adherence to the alternative treatment recommended, that prescription was deemed to be adherent to the guidelines. If the antimicrobials prescribed were not in adherence to the recommended or alternative treatment options, the researcher would then look up the antimicrobials prescribed on the list of antimicrobial medicines in chapter two of the guidelines. If the condition diagnosed was listed under the therapeutic uses for that medicine, then the prescription was deemed to be adherent to guidelines. If the antimicrobial therapy prescribed was not the same as the recommended or alternative therapy for the indication it was prescribed for, and if the indication was not listed under the therapeutic uses for that medication, then the prescription was deemed non-adherent to the antimicrobial guidelines.

3.6.2 Semi-structured interviews

The analysis for the qualitative data was carried out using QSR International's NVivo 12 Pro qualitative data analysis software (QSR International Pty Ltd., 2018). The data analysis process

began with the researcher reading the interview transcripts several times to identify key texts in the interviewees' responses to get a sense of the data. Key texts in the interview transcripts were identified in this process. The interview transcripts were imported into the NVivo software and subsequent analysis was carried out.

Text from each transcript was coded and organised into categories of related content. These categories were then analysed and relationships between the categories were identified. From these relationships, themes and sub-themes were derived and used in the interpretation of the data (Nowell et al., 2017). The researcher's interpretations of the data from the interview transcripts were prepared and recorded, and conclusions were drawn from the analysis. The interview transcripts were examined by the supervisors for this study to validate them.

3.7 Reliability and Validity

The quantitative results were collected using the SAASP antimicrobial prescription chart, which was already being adopted in healthcare facilities in South Africa, and had been used in previous studies to collect data. Because of this, the data collection method was deemed to be reliable. The qualitative results were checked by the supervisors to ensure reliability. Validity of both the quantitative and qualitative results and observations made was also measured by how these results were similar to those found in other studies done in African countries for paediatric patients.

3.8 Ethics

Ethical approval was obtained from the following: (1) the Rhodes University Faculty of Pharmacy's Ethics Committee (with the reference number PHARM-2018-09) (Appendix F); (2) the Internal Research Board at MDH (with the reference number MH/DHMT/1/7/7 (32)) (Appendix G); and (3) the Health Research and Development Division of the Ministry of Health of Botswana (with the reference number HPDME 13/18/1) (Appendix H).

This study involved the collection of retrospective data from patient files; therefore, there was no contact between the researcher and the patients. The risk level of this study was categorised by the ethics committees as low risk.

Each patient file was allocated a single study number. The patients' names and hospital numbers, which were required to identify the files, were stored in a secure, password protected

data file, accessible to the researcher and supervisors only. No other identifiable information about the patients was recorded. The data collection tool, which was the SAASP Antibiotic Prescription Chart, was designed to only record demographic data such as the age and sex of the patient and therefore no identifiable information was included on the data collection sheets.

Prospective interviewees were provided with information regarding the interviews (Appendix C) and consent forms to sign when they agreed to participate in the study (Appendix D). The interviewees were also allocated a single participant number. The names of the interviewees were kept in a secure, password protected data file, accessible only to the researcher and supervisors. The names of the interviewees did not appear on any of the interview transcripts, and the audio files of these interviews were kept in a secure password protected data file and kept in a lockable facility. The interviewees were provided with a copy of the transcript of the audio recordings for verification purposes.

The results from this study are detailed in the following chapter.

Chapter 4: Results

This chapter reports the quantitative and qualitative results of the study. The South African Antimicrobial Stewardship Programme (SAASP) Antibiotic Prescription Chart was the data collection tool used to collect the quantitative results. The qualitative results were obtained from the semi-structured interviews carried out with healthcare professionals (HCPs) at the Mahalapye District Hospital (MDH).

4.1 Information from the patient files

A total of 278 patient files were included in the analysis for this study. Of the 278 patient files, 12 patients had second admissions, i.e., they had been admitted on two separate occasions during the study period (between January 2018 and December 2018). These second admissions were recorded as separate prescriptions therefore, a total of 290 prescriptions were reviewed.

4.1.1 Patient demographics

4.1.1.1 Age

The patients' ages were divided into six categories using the age ranges specified by the National Institute of Child Health and Human Development as a guide (Williams et al., 2012). The six categories were: 0 to 27 days, 28 days to 12 months, 13 months to 24 months, 2 years to 5 years, 6 years to 11 years, and 12 years to 14 years. According to the original specifications by Williams et al (2012), the final age range is from 12 years to 18 years, but this was modified for this study as there were no patients older than 14 admitted to the paediatric ward during the study period (Figure 4.1).

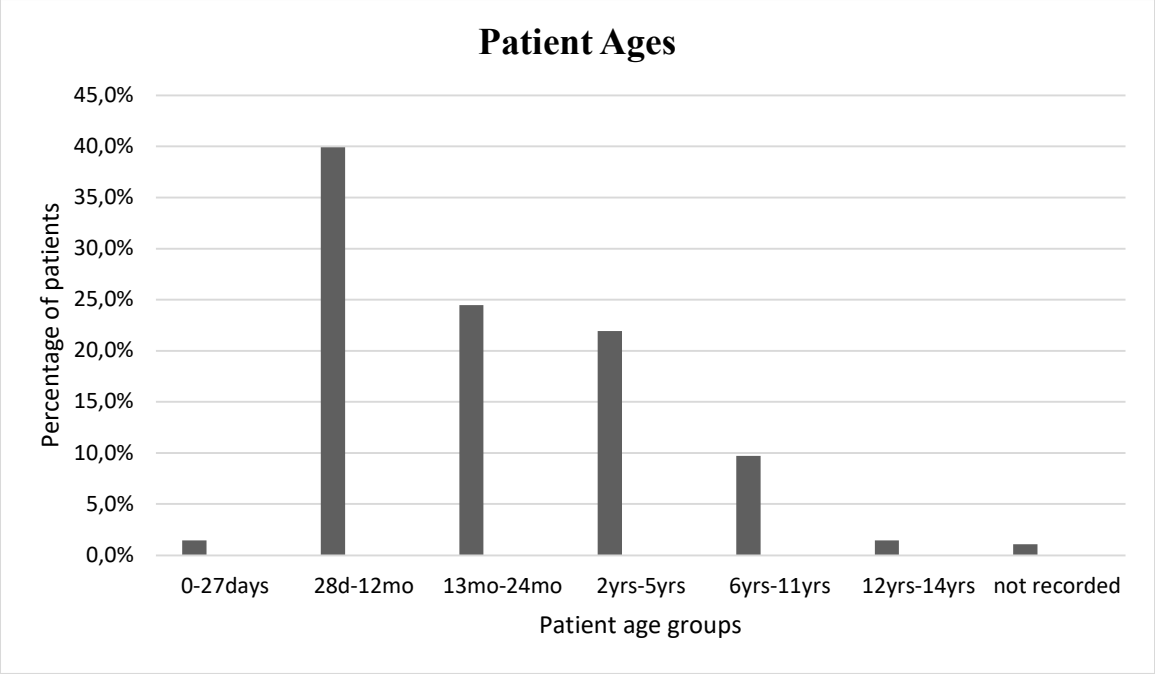


Figure 4.1: Patient ages according to specified age groups (n=278).

The age group with the highest number of patients (39.9%, n=111) was the 28 days to 12 months age group. The lowest frequency occurred in the birth to 27 days and the 12 years to 14 years age group, which each had 1.4% (n=4) patients, respectively. Of the patients in the study, 1.1% (n=3) did not have information about their age recorded in their patient files.

4.1.1.2 Sex

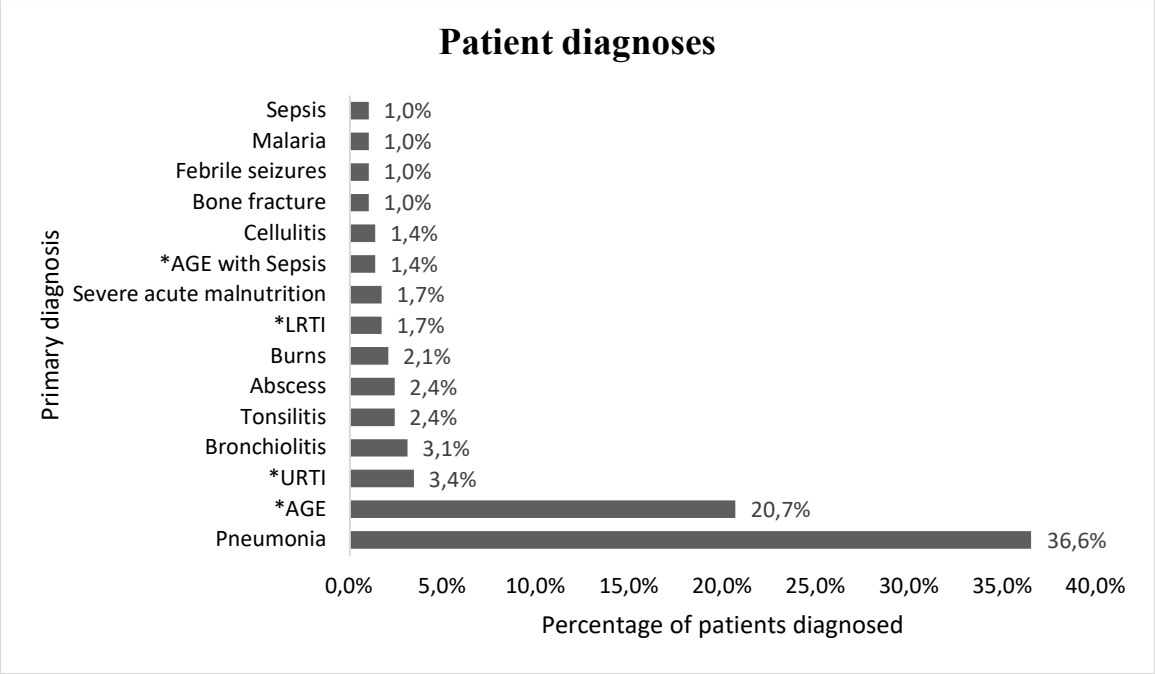
Of the 278 patients 47% (n=132) were female patients and 53% (n=146) were male patients.

4.1.2 Patients' medical information

4.1.2.1 Primary diagnoses

The most common primary diagnoses for which antimicrobial therapy was prescribed during the study period were pneumonia, acute gastroenteritis, and unspecified upper respiratory tract infections. Pneumonia was the most common primary diagnosis with 36.6% (n=106) of patients with this diagnosis. Acute gastroenteritis was the second most common diagnosis with and incidence of 20.7% (n=60), unspecified upper respiratory tract infections (URTI) were the third most common diagnosis with and incidence of 3.4% (n=10) and bronchiolitis was the fourth most common diagnosis with an incidence of 3.1% (n=9).

Fifteen primary diagnoses made up 81.0% (n=235) of all the primary diagnoses, as seen in Figure 4.2.

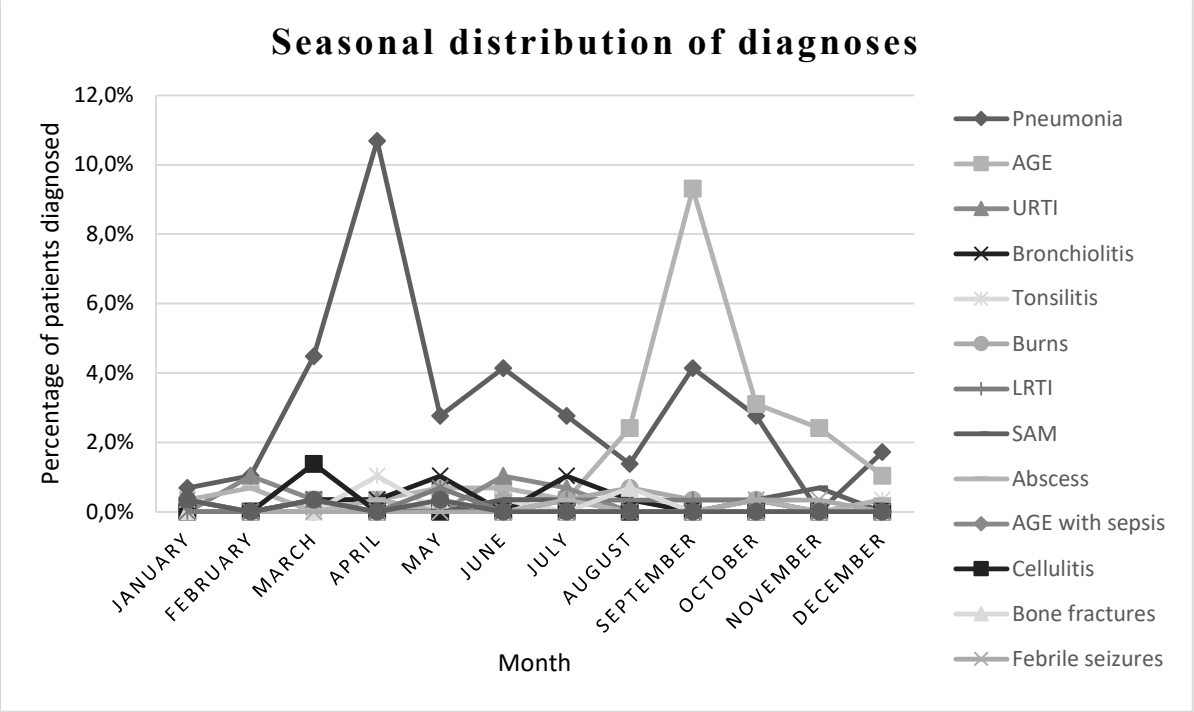


(*AGE – Acute gastroenteritis; *URTI – Upper respiratory tract infection; *LRTI – Lower respiratory tract infection)

Figure 4.2: The 15 most common primary diagnoses for which antimicrobial therapy was prescribed (n=290).

4.1.2.2 Seasonality of infections

These diagnoses where analysed to see if there was any seasonality in their incidence (Figure 4.3). The majority were evenly distributed throughout the year – as can be seen by the many lines close to the X-axis, except pneumonia and AGE which seemed to have a seasonal peak.



(AGE – Acute gastroenteritis; URTI – Upper respiratory tract infection; LRTI – Lower respiratory tract infection; SAM – Severe acute malnutrition)

Figure 4.3: Seasonal distribution of incidence of the most common diagnoses between January and December 2018 (n=290).

The diagnoses which showed higher incidences during specific periods of the year were presented in a separate graph (Figure 4.4). Pneumonia was the only diagnosis that showed seasonality.

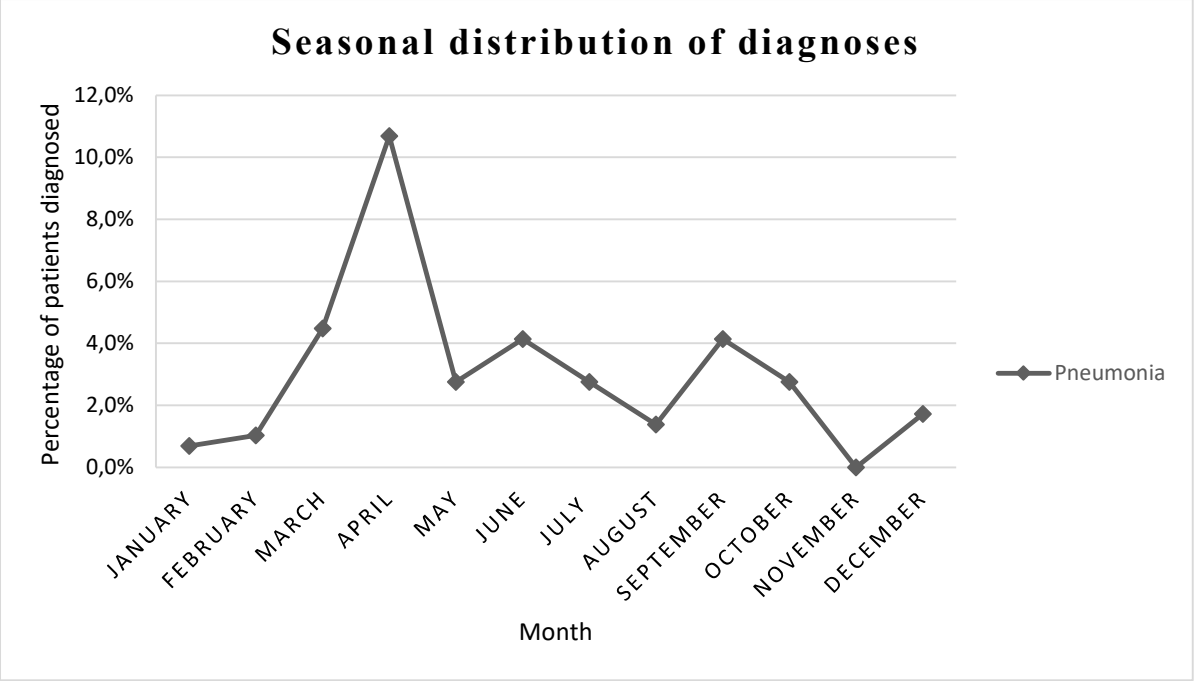


Figure 4.4: Distribution of incidence of pneumonia during the study period of January to December 2018 (n=290).

The highest incidence of pneumonia occurred in April, while the lowest was in January, February, and October.

4.1.2.3 Source of infection

The source of infection was classified as either community acquired, or hospital acquired. These designations were defined according to the SAASP Antibiotic Prescription Chart, which defines community acquired infections as infections that occur "within 48 hours of admission to hospital", and hospital acquired infections as infections that occur "more than 48 hours after admission or within 30 days of discharge" from the hospital (South African Antibiotic Stewardship Programme, 2014, p. 1). Using these definitions, 98.3% (n=285) of the prescriptions analysed were for community acquired infections (CAIs).

During the study period one patient (0.3%) was admitted with infections which were treated with antimicrobial medicines less than 30 days after a previous hospital admission. Two patients (0.7%) were admitted with conditions that did not require antimicrobial treatment, but they developed infections during their hospital stay. Two patients (0.7%) who were admitted with non-infectious conditions and treated prophylactically with antibiotics subsequently developed infections. These were all classified as hospital acquired infections (HAIs).

Table 4.1 shows the hospital acquired infections (HAIs) that occurred in the study population during the study period.

Table 4.1: Hospital acquired infections during study period (n=5).

Description of hospital acquired infections (HAIs)	**Number of patients**	**Initial diagnosis**	**Diagnosis of HAI**	**Treatment prescribed**
Patients who developed infections <30 days after discharge from hospital.	1	a. HIV exposure	Acute gastroenteritis with sepsis	• Ampicillin • Gentamicin • Ceftriaxone • AZT • Cotrimoxazole
Patients who did not require antimicrobial treatment initially who developed infections.	2	a. Severe wasting malnutrition	Lower respiratory tract infection (LRTI)	• Amoxicillin • Cefpodoxime
		b. Acute gastroenteritis	LRTI	• Ampicillin • Gentamicin
Patients initially admitted with non-infectious conditions and treated with antimicrobial prophylaxis.	2	a. Partial thickness burns	Pneumonia	• Cefuroxime
		b. Severe acute malnutrition and anaemia	Sepsis	• Cefuroxime

4.1.2.4 HIV Status

The majority of patients were below the age of 5 years; hence the HIV status was usually stated in the patient files with reference to HIV exposure at birth.

According to the 'Handbook of the Botswana 2016 Integrated HIV Clinical Care Guidelines', all babies exposed to HIV at birth are required to undergo a DNA Polymerase Chain Reaction (PCR) test by the age of 6 weeks (Botswana Ministry of Health, 2016). The guidelines further state that "All children identified as negative by 6 weeks, who are not breastfed, must undergo

rapid HIV testing at 18 months. All children identified as negative by 6 weeks, who are breastfed, should have repeat HIV testing 6 weeks after cessation of breastfeeding" (Botswana Ministry of Health, 2016, p. 6). The patients' HIV status was recorded in their files using the following terminology:

Table 4.2 Definitions of terms used to describe patient HIV status.

Term used	Description of the term
HIV Exposed (HE)	Patients who were exposed to HIV at birth. These patients were taking prophylactic doses of antiretroviral (ARV) medication and had not undergone PCR testing yet.
HIV Exposed, Uninfected (HEU)	Patients who were exposed to HIV at birth and had a PCR test with the results being negative. This included patients who had a rapid HIV test at 18 months or 6 weeks after cessation of breastfeeding.
HIV Negative	Patients who had a rapid HIV test with the result being negative.
HIV Positive	Patients who had been tested and confirmed to be HIV positive.
HIV Unexposed (HU)	Patients who were not exposed to HIV at birth.
Unknown	Patients whose HIV status was unknown or undocumented in their patient file.

The HIV status of each patient was recorded to determine whether they had any influence on prescribing practices at MDH. They were described using the terms defined in Table 4.2 and shown in Figure 4.5. Half of the patients (50.0%, n=139) were unexposed to HIV. From the patients exposed to HIV at birth, 19.1% (n=53) had a negative PCR test result and were defined as HEU, and 4.3% (n=12) were awaiting PCR testing and were defined as HE. Three (1.1%) of the patients were HIV positive, and 9.4% (n=26) were HIV negative. Patients whose HIV status was unknown made up 16.2% (n=45) of the study population.

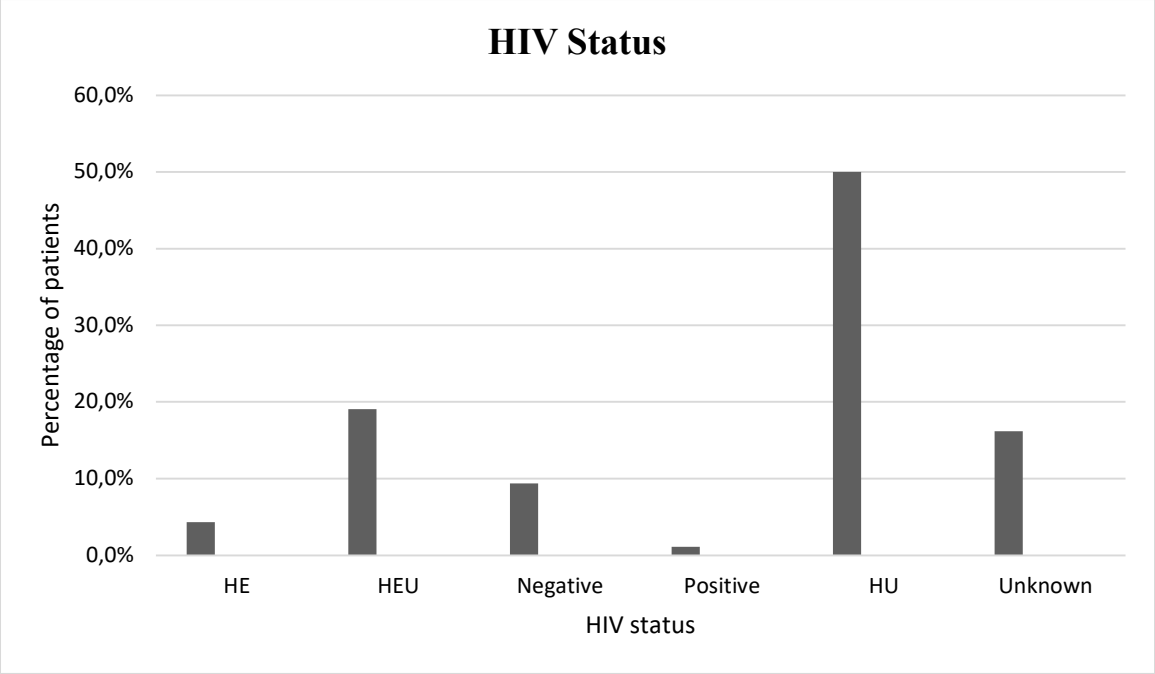


Figure 4.5: Distribution of patients' HIV status (n=278).

4.1.3 Antimicrobial Prescribing

4.1.3.1 Antimicrobial prescribing during the study period

A total of 659 antimicrobial medicines were prescribed during the study period. Of these, 0.3% (n=2) were antifungals; 1.1% (n=7) were antimycobacterials; 1.1% (n=7) were antiplasmodials; 0.6% (n=4) were antiretrovirals and 0.2% (n=1) were antivirals. The rest of the medicines prescribed were antibiotics (96.8%, n=638), as indicated in Table 4.3. The mean number of antimicrobials per patient was 2.

Table 4.3 Classes of antimicrobial medicines prescribed (n=659) and their frequency.

Antimicrobial type	Frequency
Antibiotic	
Amikacin	5
Amoxicillin	40
Amoxicillin-clavulanic acid	50
Ampicillin	141
Cefotaxime	53
Cefpodoxime	34
Ceftriaxone	21

Cefuroxime	32
Cloxacillin	16
Cotrimoxazole	12
Erythromycin	17
Gentamicin	140
Metronidazole	25
Nalidixic Acid	12
Phenoxymethylpenicillin	2
Piperacillin-tazobactam	5
Vancomycin	33
Total	**638**
Antifungal	
Griseofulvin	1
Miconazole	1
Total	**2**
Anti-mycobacterial	
Ethambutol	2
RHZ	3
RHZE	2
Total	**7**
Anti-plasmodial	
Artemether/ Lumefantrine	2
Artesunate	3
Primaquine	2
Total	**7**
Antiretroviral	
Abacavir	1
Efavirenz	1
Lamivudine	1
Zidovudine	1
Total	**4**
Antivirals	

Acyclovir	1
Total	**1**
Total	**659**

(RHZ – Rifampicin, Isoniazid, Pyrazinamide combination; RHZE - Rifampicin, Isoniazid, Pyrazinamide, Ethambutol combination.)

Since most of the antimicrobial medicines prescribed were antibiotics, these were further analysed and separated into their different classes. The penicillins were the most prescribed class of antibiotics, making up 39.8% (n=254) of all the prescriptions. Aminoglycosides and cephalosporins made up 22.7% (n=145) and 21.9% (n=140) of all the prescriptions, respectively. The quinolone antibiotics were the least prescribed, with nalidixic acid being the only one prescribed in that class with 1.9% (n=12) of all the prescriptions.

Table 4.4 Classes of antibiotics prescribed (n=638) and their frequency

Antibiotic class	Frequency
Penicillins	
Amoxicillin	40
Ampicillin	141
Amoxicillin-clavulanic acid	50
Cloxacillin	16
Phenoxymethylpenicillin	2
Piperacillin-tazobactam	5
Total	**254**
Aminoglycosides	
Amikacin	5
Gentamicin	140
Total	**145**
Cephalosporins	
Cefotaxime	53
Cefpodoxime	34
Ceftriaxone	21
Cefuroxime	32
Total	**140**
Glycopeptides	

Vancomycin	33
Total	**33**
Macrolides	
Erythromycin	17
Total	**17**
Quinolones	
Nalidixic Acid	12
Total	**12**
Other	
Cotrimoxazole	12
Metronidazole	25
Total	**37**
Total	**638**

The most prescribed antimicrobials were ampicillin and gentamicin, which constituted 21.4% (n=141) and 21.2% (n=140) of all the antimicrobial prescriptions in the analysed prescriptions, respectively. The third most prescribed antimicrobial was cefotaxime, which made up 8.3% (n=53) of the antimicrobial prescribed. The top 10 most frequently prescribed antimicrobials, as displayed in Figure 4.6, were all antibiotics.

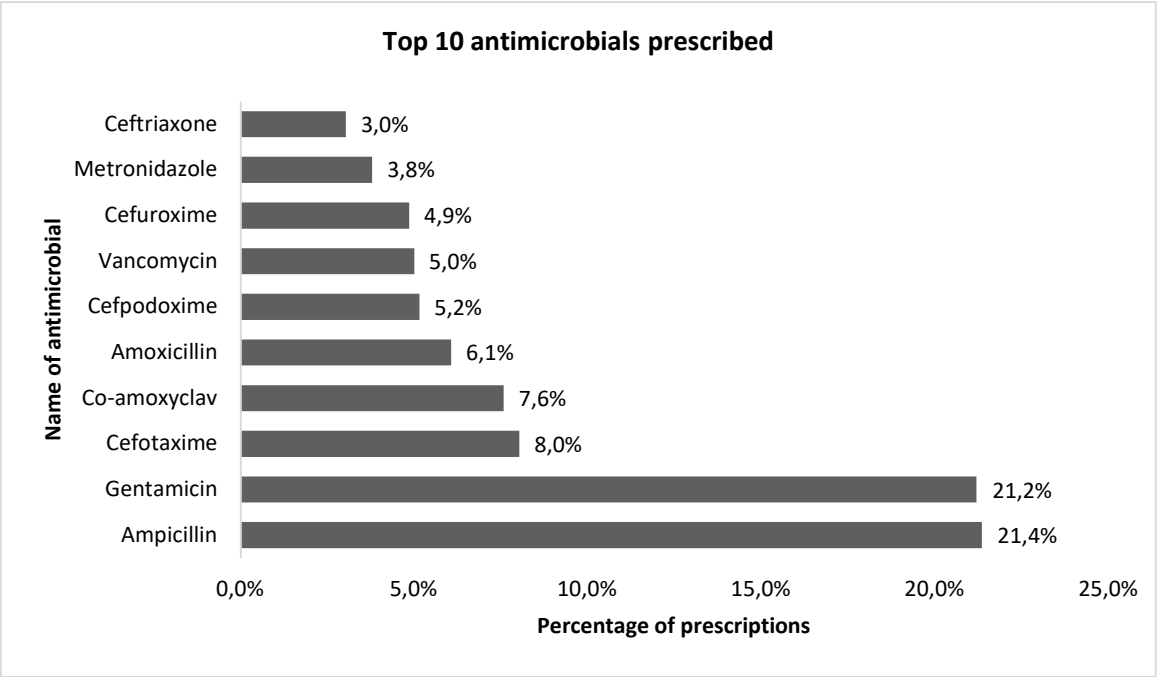


Figure 4.6: Top 10 most frequently prescribed antimicrobials (n=659 is the total number of antimicrobials prescribed).

Of the admissions included in the study, 60.0% (n=174) had antimicrobial combinations, meaning that they had more than one antimicrobial prescribed during the same period. The most common combinations of antimicrobials prescribed are displayed in Figure 4.7. The most frequently prescribed antimicrobial combination was ampicillin and gentamycin, which was found in 30.3% (n=88) of the admissions included in the study.

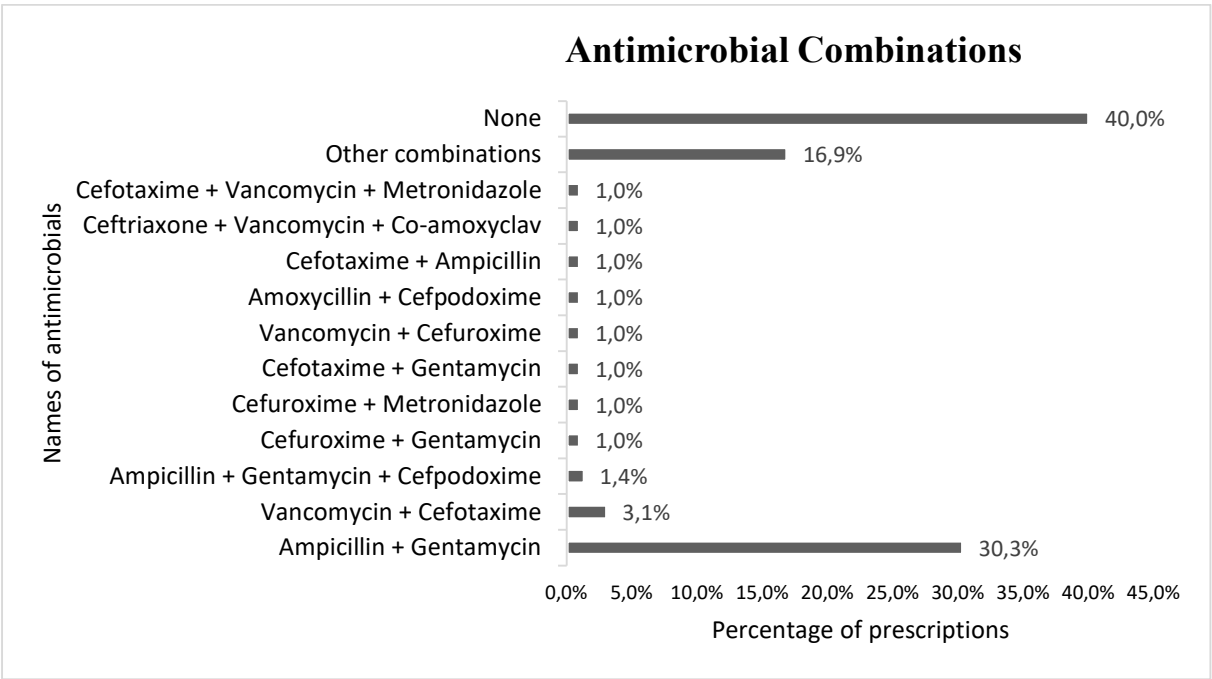


Figure 4.7: The most frequently prescribed antimicrobial combinations (n=290).

4.1.3.2 Route of administration

A high proportion of the antimicrobials prescribed in this study was administered parenterally (69.5%, n=458). This is not surprising considering the main route of administration of many of the most prescribed antimicrobials is the parenteral route (Rossiter et al., 2016). A smaller proportion of the medicines were administered to patients orally (25.0%, n=165). Some of the medicines prescribed were not given to patients due to one of the following reasons: either the medicine was out of stock or failure to insert a cannula for parenteral medicines (5.5%, n=36). (Figure 4.8)

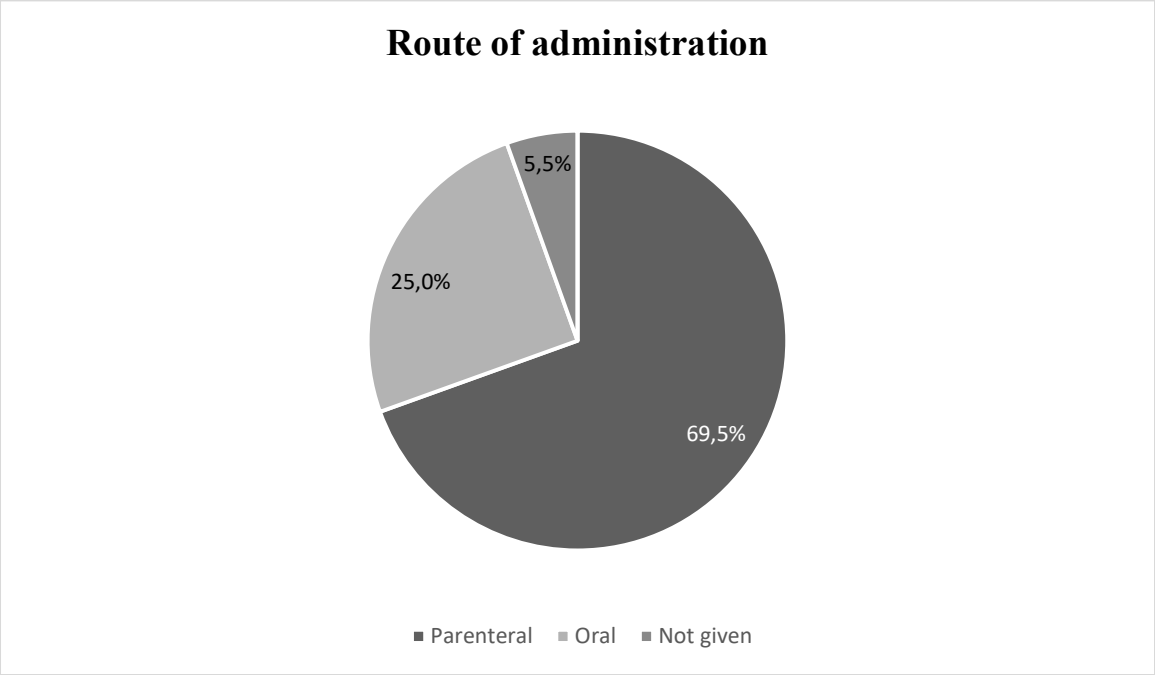


Figure 4.8 Distribution of routes of administration of antimicrobials (n=659).

4.1.3.3 Indication of treatment

278 patient files were included in this study, 12 of which had second admissions recorded which made up a total of 290 patient admissions in the study. Of the 290 patient admissions, 16.9% (n=49) had microbiological samples taken and sent to the laboratory for Microbial Culture and Sensitivity (MCS) testing.

Regarding the indication of treatment: 83.1% (n=548) of the antimicrobial prescriptions were empiric, 1.7% (n=11) were definitive and MCS directed; and 15.2% (n=100) were prophylactic (Figure 4.9).

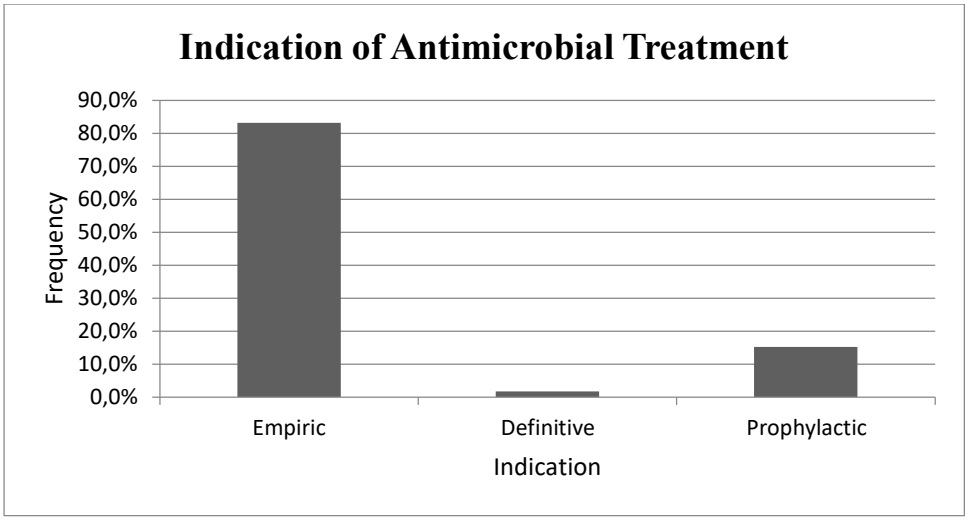


Figure 4.9 Indication of antimicrobial treatment (n=659)

4.1.3.4 Duration of therapy

Duration of treatment was grouped into the following categories as done in a previous similar study: <5 days, 5-7 days, 8-10 days and >10 days (Johnston et al., 2018). Where antibiotics were prescribed but not administered to the patient, either due to the medicine in question being out of stock or failure to administer (for example, where a cannula was not inserted for intravenous administration), this was recorded as "not given" (Figure 4.10).

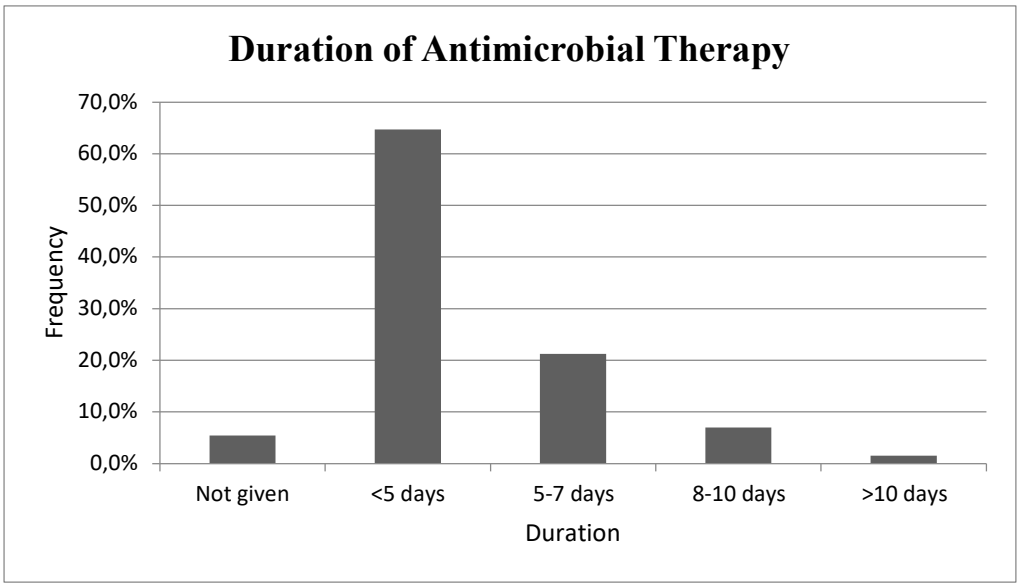


Figure 4.10 Duration of antimicrobial therapy (n=659).

The majority of antimicrobial therapy was administered for less than five days (n=427, 64.7%). Of the antimicrobials prescribed, 21.2% (n=140) administered for five to seven days, and 7.0%

(n=46) administered for eight to ten days. 1.5% (n=10) of the antimicrobials were administered for more than ten days. Of the antimicrobials prescribed, 5.5% (n=36) were not given.

According to the Botswana prescribing guidelines, to determine the duration of antimicrobial therapy, both the prescribing guidelines and the clinical response should be considered (Botswana Ministry of Health, 2012). The guidelines do not specify duration of treatment for all antimicrobials and for all infectious conditions. Below are examples of the recommended duration of treatment according to the Botswana prescribing guidelines (Table 4.5).

Table 4.5: Recommended duration of treatment according to the Botswana guidelines (Botswana Ministry of Health, 2012).

Medication	Indication	Recommended duration
Amoxicillin	Acute Otitis Media	7 days
Amoxicillin	Sinusitis	21 days
Amoxicillin-clavulanate	Sinusitis	21 days
Amoxicillin-clavulanic acid	Acute Suppurative Sialadenitis	7 - 10 days
Amoxicillin-clavulanic acid	UTI	5 days
Amoxicillin-clavulanic acid	Bites	5 -7 days
Azithromycin	AGE	3 days
Cefotaxime	Quinsy	14 days
Cefotaxime	Acute Epiglottitis	7 days
Cefotaxime	Retropharyngeal/Parapharyngeal Cellulitis/Abscess	7 - 10 days
Cefotaxime	UTI	10 - 14 days
Cefotaxime	Enteric fever	10 - 14 days
Cefotaxime	Meningitis	2 days
Cefradine	Acute Tonsillar Pharyngitis	10 days
Ceftriaxone	Acute Epiglottitis	7 days
Ceftriaxone	Spontaneous bacterial peritonitis	7 - 10 days
Clarithromycin	Acute Otitis Media	7 days
Clarithromycin	Pertussis	14 days
Ciprofloxacin ear drops	Suppurative otitis media	10 days
Cotrimoxazole	Pneumonia	7 days
Erythromycin	Acute Tonsillar Pharyngitis	10 days
Erythromycin	Acute Otitis Media	5 days

Erythromycin	Pertussis	14 days
Metronidazole	AGE	5 - 10 days
Metronidazole	AGE	7 - 10 days
Nalidixic acid	UTI	5 days
Nalidixic acid	AGE	5 days
Nitrofurantoin	UTI	5 days
Vancomycin	AGE	7 - 10 days
Vancomycin	Meningitis	2 days

(AGE – Acute gastroenteritis; UTI – Urinary tract infection)

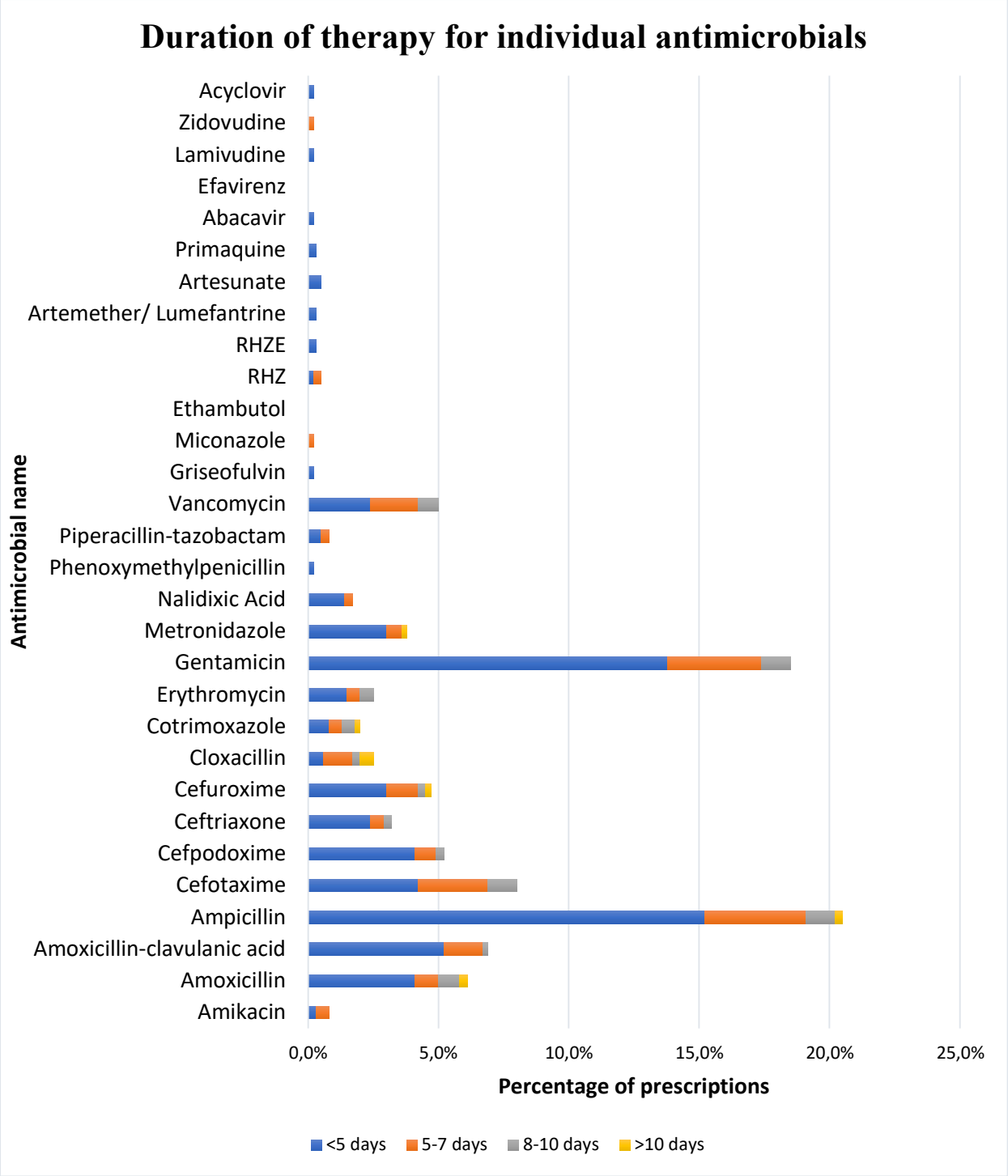


Figure 4.11 Duration of therapy for individual antimicrobials (n=659).

The specific duration for which individual antimicrobial medications were prescribed are graphically represented in Figure 4.11. Regarding the antimicrobials with specified duration of treatment according to guidelines, amoxicillin and amoxicillin-clavulanic acid were prescribed within the limits recommended in the guidelines. According to Table 4.5, the recommended duration of therapy for these antimicrobials was, for the most part, between five to ten days,

except for 21 days for sinusitis. In this study, the duration of treatment was largely within the recommended range with only 5.0% (n=2) of the amoxicillin prescriptions going above ten days, and all the amoxicillin-clavulanic acid prescriptions (90.0%, n=45) that were administered being given for five to ten days (Figure 4.11) (The rest of the prescriptions were not given (10.0%, n=5). Cefotaxime was recommended for durations ranging between seven and fourteen days by the guidelines. In this study, 52.8% (n=28) of the prescriptions were given for less than 5 days, while 34.0% (n=18) were given for five to seven days and 13.2% (n=7) were given for eight to ten days. Metronidazole was mostly given for less than 5 days (80.0%, n=20), while 16.0% (n=4) of the prescriptions were for five to seven days and 4.0% (n=1) given for more than ten days. Metronidazole was recommended for a range of five to ten days in the prescribing guidelines.

4.1.3.5 Adherence to national prescribing guidelines

Of the 659 antimicrobials prescribed during the study period, 82.7% (n=545) were found to be in compliance with the Botswana Antimicrobial Therapy Guide (Botswana Ministry of Health, 2012). It was found that 29.5% (n=82) of the patients included in the study had at least one antimicrobial medicine prescribed to them where the prescriber had not adhered to the guidelines. These antimicrobials made up 17.3% (n=114) of the total number of antimicrobial medicines prescribed to patients in this study.

Table 4.6 includes examples of prescriptions where prescribers had not adhered to the Botswana antimicrobial prescribing guidelines.

Table 4.6 Examples of antimicrobial prescriptions which did not adhere to guidelines (Botswana Ministry of Health, 2012).

Patient details				
Age	**Indication for treatment**	**Antimicrobials prescribed**	**Duration of therapy**	**Recommended treatment according to guidelines**
6 years	Traumatic amputation	Gentamicin 90mg IV od	3 days	Cefradine 25-200mg/kg in 4 divided doses. Max 4g/day
1 year 3 months	Superficial knee abscess	Metronidazole 75mg IV tds	7 days	Amoxicillin-clavulanic acid 40-90mg/kg in 3 divided doses
1 year 6 months	Abscess and dermatitis	Ampicillin 140mg IV tds Gentamicin 40mg IV od Metronidazole 120mg IV bd	3 days	Amoxicillin-clavulanic acid 40-90mg/kg in 3 divided doses
11 years	Surgical prophylaxis	Gentamicin 80mg IM od Tazobactam (strength not recorded) IV od	6 days 3 days	Cefradine 1-2g IV (single dose, re-dose if necessary)
6 years	Pneumonia	Ampicillin 800mg IV qid Gentamicin 85mg IV od	3 days	Amoxicillin + Clavulanic acid IV 50-80mg/kg/day divided 8-hourly, **OR** Cefuroxime IV 150mg/kg/day divided 8-hourly, **OR** Cefotaxime 150mg/kg/day divided in 3 doses given 8-hourly
1 year 9 months	Pneumonia	Metronidazole 77mg IV tds	7 days	Amoxicillin + Clavulanic acid IV 50-80mg/kg/day divided 8 hourly, **OR** Ampicillin IV 200mg/kg/day (max. 4g) divided 6 hourly + Gentamicin IV 5mg/kg daily y, **OR** Cefuroxime IV 150mg/kg/day divided 8 hourly, **OR** Cefotaxime 150mg/kg/day divided in 3 doses given 8 hourly.
7 months	Pneumonia	Amikacin 90mg IV od	5 days	Same as above

9 months	AGE	Cotrimoxazole (strength not recorded) PO bd	3 days	Oral rehydration therapy Ampicillin 250mg 4-6 hourly IV (Infusion/Injection), **OR** Erythromycin 50mg/kg/day (by continuous IV infusion)
1 month	Omphalitis	Cloxacillin 250mg PO qid Cefuroxime 250mg IV tds Metronidazole 64mg IV tds	7 days 6 days 6 days	Gentamicin 5mg/kg/dose q24h+ Clindamycin 15mg/kg/day divided 8-hourly
2 years	Burns	Cefotaxime 200mg IV tds	8 days	Cloxacillin 500mg PO once, **OR** Clindamycin 600mg PO once

(AGE – acute gastroenteritis; IV – intravenous; IM – intramuscular; PO – orally; od – once daily; bd – twice daily; tds – three times daily; qid – four times daily;

Of the prescriptions where guidelines had not been followed, the classes of antimicrobials were as follows: the majority were for penicillins (37.7%, n=43), followed by aminoglycosides (21.9%, n=25) and metronidazole (16.7%, n=19) This is shown in Figure 4.12.

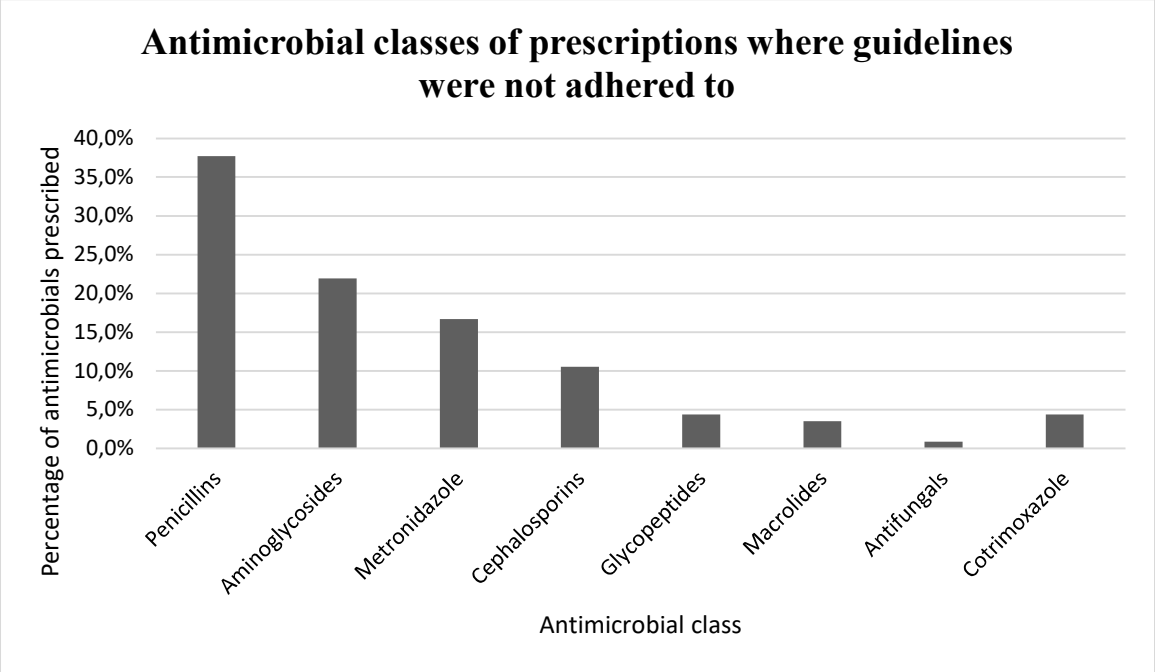


Figure 4.12 Distribution of antimicrobial classes in prescriptions where guidelines were not adhered to (n=114).

The individual antimicrobials were analysed separately as shown in Figure 4.13. Ampicillin was the most common antimicrobial in this group, making up 20.2% (n=23) of the prescriptions where prescribers had not adhered to guidelines.

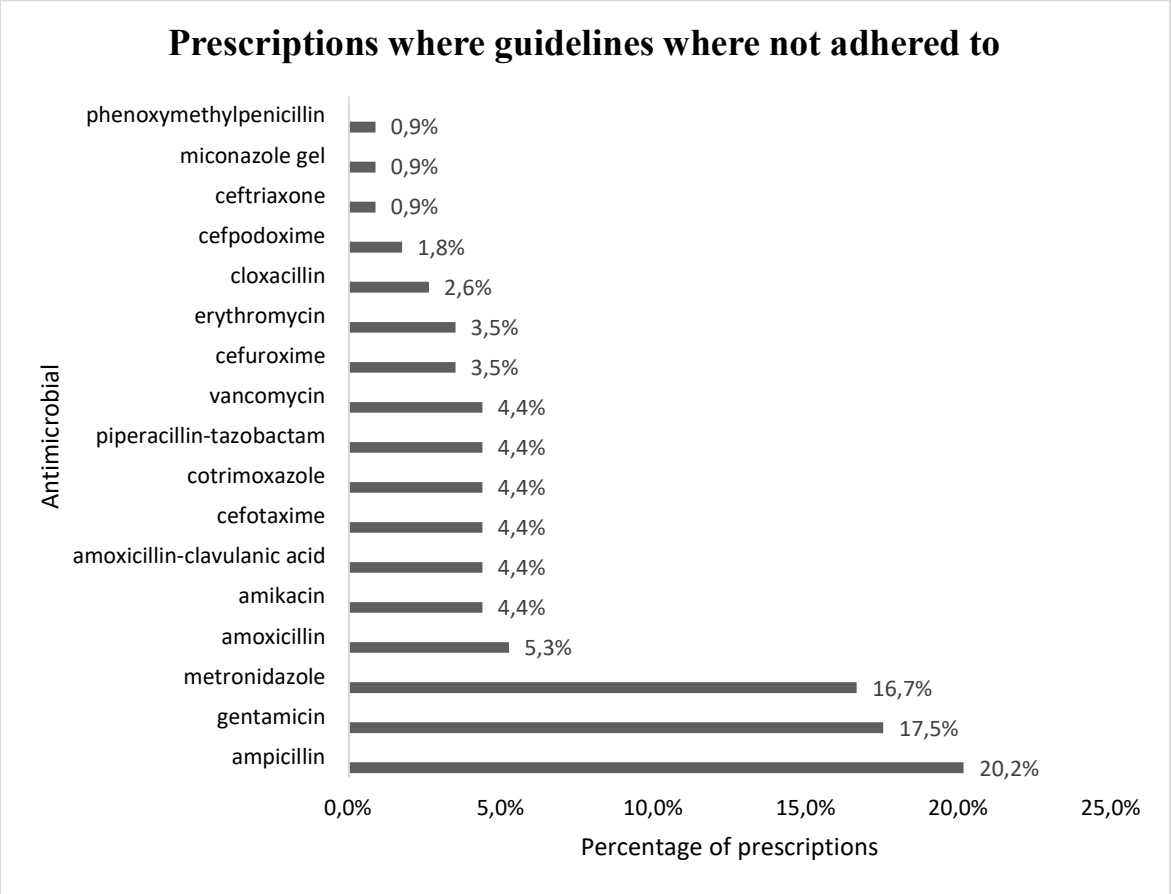


Figure 4.13 Distribution of antimicrobials prescribed where guidelines where not adhered to (n=114).

The highest number of instances where prescribers had not adhered to guidelines occurred in children between 28 days and 12 months, as can be seen in Figure 4.14.

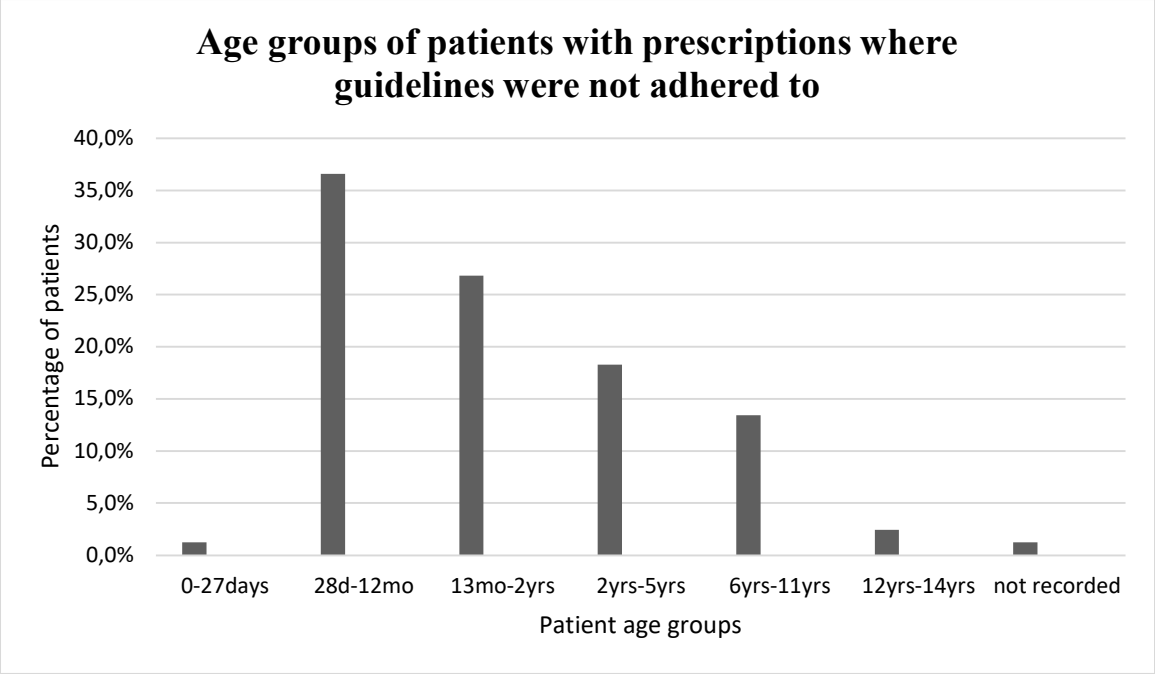


Figure 4.14 Patient age groups and antimicrobial prescriptions where guidelines were not adhered to (n=82).

Interestingly none of the HIV-positive patients received antimicrobial treatments where guidelines had not been adhered to.

The following section reports the results of the semi-structured interviews which make up the qualitative portion of the study.

4.2 Results from the semi-structured interviews

The objectives of this study included determining whether there was an Antimicrobial Stewardship Committee and whether there were factors which influenced antimicrobial prescribing practices at Mahalapye District Hospital (MDH). To obtain this information, semi-structured interviews were conducted with a medical doctor, a registered nurse, and a pharmacist who were employed at MDH at the time of the study.

The interviews were transcribed and analysed by the researcher using QSR International's NVivo 12 Pro qualitative data analysis software (QSR International Pty Ltd., 2018). The interview transcripts were examined by the supervisors for this study to validate them.

4.2.1 Thematic analysis

To analyse the transcribed data, the individual phrases and responses of the participants were labelled according to the subject matter being discussed. These labels are referred to as codes and are listed in Table 4.7. The labels were then analysed and given themes i.e., the themes offer further explanation of the issues that the codes refer to. The codes and themes identified were analysed and categories emerged. The codes and themes were placed into one of three categories, namely:

1. Knowledge about AMS committee, guidelines, protocols, SOPs, policies, and procedures
2. Perceived challenges experienced by clinical staff, or
3. Opinions about the AMS committee, guidelines, protocols, SOPs, policies, and procedures

Table 4.7 contains the codes, themes, and categories that were identified during the thematic analysis.

Codes	Themes	Categories
• Members and function of AMS committee	*Knowledge of the existence and function of an AMS committee*	**1. Knowledge about AMS committee, guidelines, protocols, SOPs, policies, and procedures**
• Autonomy • Reporting structures • Structure and functioning • Training of members • Responsibilities of members	*The functioning of the AMS committee*	
• Communication between hospital leadership and staff on AMS	*Knowledge of policies and programmes in the hospital to control the prescribing of antimicrobials*	

• Process of authorisation of antimicrobials • Policies and procedures regarding the rational use of antimicrobials		
• National and local guidelines used at the hospital • Protocols for prescribing and selection of antimicrobials • SOPs for prescribing and administering antimicrobials to paediatric inpatients	*Knowledge of the antimicrobial prescription guidelines, protocols and SOPs used in the paediatric ward*	
• Laboratory turnaround time • Absence of a paediatrician on AMS committee	*Challenges that affect the AMS committee and the prescribing of antimicrobial medicines*	**2. Perceived challenges experienced by the AMS and prescribers**
• Necessity of an AMS committee at MDH	*Whether they think there is a need for an AMS committee at MDH*	**3. Opinions about the AMS committee**
• What interviewees think about the structure and function of the AMS committee • What interviewees think about the responsibilities of	*Opinions about the functions and responsibilities of the AMS committee*	

members of the AMS committee • What interviewees think about the role of institutional pharmacists in the AMS committee		

The categories, themes and codes will be discussed in detail in the Discussion chapter. The next chapter discusses all the results.

Chapter 5: Discussion

This chapter is a discussion of the results presented in Chapter 4 in relation to the research objectives and relevant literature.

The aim of the study was to investigate the antimicrobial prescribing practices in the paediatric medical ward (PMW) at Mahalapye District Hospital (MDH) to determine whether antimicrobials were being prescribed rationally and in accordance with the national guidelines. The study also aimed to determine whether there were antimicrobial stewardship (AMS) measures being implemented at MDH.

5.1 Demographic information

Most of the patients were younger than 5 years and the age group with the highest number of patients was the 28 days to 12 months age group (39.9%). The age groups with the least number of patients were the zero to 27 days and the 12 to 14 years age groups (1.4%, respectively). There were slightly more males (53%) than females (47%) in the PMW but this had no significance on the data since antimicrobial prescribing for children is usually based on age or weight, and not height or sex (Mathur et al., 2020).

5.2 Disease Epidemiology

5.2.1 Incidence of disease

The most common diagnoses were pneumonia (36.6%), acute gastroenteritis (AGE) (20.7%), upper respiratory tract infections (URTIs) (3.4%) and bronchiolitis (3.1%). Of these, pneumonia was the most prevalent, with 36.6% of patient admissions being for pneumonia. In a study carried out on paediatric patients in Ethiopia, the results were similar in that pneumonia was the most prevalent diagnosis, but differed in the subsequent diagnoses, where their study had severe acute malnutrition and meningitis as the second and third most common diagnoses, respectively (Girma et al., 2018). Another study carried out on paediatric patients in Botswana had similar results to ours, where pneumonia and AGE were the most common diagnoses (Fisher et al., 2009). Chandra et al. (2014) had similar results, where pneumonia and diarrhoea were the most common diagnoses in children under 5 years old, and gastrointestinal disorders

and pneumonia were among the commonest diagnoses in children between 5 years and 14 years old.

5.2.2 Seasonal variations of disease

Regarding seasonality of infections pneumonia showed seasonality in its distribution. Pneumonia incidence peaked in April and was irregular but remained high relative to other diagnoses through May to October. This result was similar to a study done by Kelly et al., (2015), which showed that pneumonia incidence among children in Botswana peaked between March and July. Results from a study done in Kenya by Tornheim et al. (2007) indicated that pneumonia incidence in children under 5 was highest in the months of January to February and June to August, approximately two to three months after each rainy season. Interestingly, pneumonia incidence increased at MDH in the winter months, which fall before the rainy season in Botswana (Statistics Botswana, 2018). Le Roux et al. (2015) showed that in South Africa pneumonia incidence in paediatric patients was higher in the winter months. Pneumonia incidence at MDH was higher in the winter months and this seems to be consistent with the findings from other African countries.

5.2.3 Source of infection

Almost all the patients (98.3%) in this study were admitted with community acquired infections, which is defined as "infections that occur within 48 hours of admission to hospital" (South African Antibiotic Stewardship Programme, 2014, p. 1). However, five patients developed hospital acquired infections (HAIs) during their hospital stay. Two of these patients were initially admitted with conditions that did not require antimicrobial treatment and subsequently developed infections while in hospital. Two others were admitted and treated prophylactically with antimicrobial medicines and developed infections during their hospital stay. Another patient was admitted, treated with antimicrobial medicines, discharged from hospital, and was readmitted with an infection within 30 days of being discharged from hospital. The incidence of HAIs could have been due to transmission between patients, or from healthcare professionals. Such infections can be prevented through infection control measures (Murni et al., 2015). The total number of patients who were diagnosed with HAIs during the study period was five (1.7%). This was low compared to other studies conducted in other African countries, namely a South African study by Olivier et al. (2018) and a Nigerian study by Abubakar (2020) which reported HAI incidences of 9.9% and 14.3% respectively. It is

important to note that these studies were point prevalence studies conducted in multiple centres, therefore the higher rates they report may be a result of larger sample size. However, when compared to another study conducted in a single hospital in South Africa with a similar sample size of 326 patients which reported an HAI rate of 7.67%, the rate of HAIs at MDH was still low (Nair et al., 2018).

5.2.4 HIV status

Half of the patient population in this study had not been exposed to HIV at birth i.e., were classified as "HIV unexposed (HU)". The second most commonly occurring HIV status was patients who had been exposed to HIV at birth but were not infected i.e., classified as "HIV exposed, uninfected (HEU)", which accounted for 19.1% of all patients in the study.

Botswana is one of the countries with the highest number of HEU children globally, with an estimated 27.4% of all HEU children living in Botswana (Slogrove et al., 2020). HIV status was unknown for 16.2% of all the patients whose files were analysed during this research. Three (1.1%) of the patients were known to be HIV-positive, and 26 (9.4%) were confirmed HIV-negative.

Slogrove et al. (2020) and Zash et al. (2016) have shown that HIV exposure tends to lead to higher morbidity and mortality in paediatric patients. However, in this research patients who had not been exposed to HIV at birth (HU) accounted for the majority of patients (55.7%) and infections.

5.3 Antimicrobial prescribing

5.3.1 Distribution of antimicrobials prescribed

A total of 659 antimicrobial medicines were prescribed for the 278 patients whose files were included in this study. These included antibiotics, antifungals, antimycobacterials, antiplasmodials, and antivirals. Most of the antimicrobials prescribed were antibiotics. This was consistent with results found in a worldwide study done by Versporten et al. (2016) and a South African study by Koopmans et al. (2018), which also found antibiotics to be the most prescribed antimicrobials.

In this research the most prescribed antimicrobials were ampicillin (21.4%) and gentamycin (21.2%) and were often prescribed as a combination. This is not unusual as the combination of

gentamicin with ampicillin can be used synergistically for the treatment of serious infections such as infections caused by enterococci and is recommended for such use in the Botswana guidelines (Botswana Ministry of Health, 2012). In a worldwide study, ampicillin and gentamicin were ranked the most prescribed medicines in paediatric patients, with Africa being one of the regions where gentamicin was used most frequently (Versporten et al., 2016). This supports our findings, and the similarity could be due to similar incidences of infection or prescribing practices in African countries.

Also among the ten most prescribed antimicrobials were cefotaxime (8.0%), amoxicillin-clavulanic acid (7.6%), amoxicillin (6.1%) cefpodoxime (5.2%), vancomycin (5.0%), cefuroxime (4.9%), metronidazole (3.8%) and ceftriaxone (3.0%), which are broad-spectrum antibiotics. A study conducted in Ghana on paediatric patients reported prevalent use of third-generation cephalosporins such as ceftriaxone (14.9%) and cefuroxime (12.4%) in higher proportions compared to our study (Labi et al., 2018). The same study showed similar rates of amoxicillin-clavulanic acid use (6.9%) to our study. According to Versporten et al. (2016) high rates of broad-spectrum antibiotic use are an important indicator of quality in prescribing for paediatrics. The use of broad-spectrum antimicrobials has been associated with the proliferation of the development of AMR, and the use of narrow-spectrum antimicrobials where possible is recommended (Centers for Disease Control, 2019; Dellit et al., 2007; Hawkey et al., 2018).

5.3.2 Route of administration

A large proportion of the antimicrobials prescribed in this study were administered parenterally (69.5%). This result was similar to that shown in a South African hospital, which found that 72% of antimicrobial medicines in the paediatric medical ward were given parenterally (Koopmans et al., 2018). The reasons for the high use of parenteral antimicrobials could include: younger or severely ill patients not being able to take oral medications, severity of illness, some antimicrobials being exclusively parenteral formulations and better bioavailability associated with parenteral formulations compared to oral (Amadeo et al., 2010). Switching from parenteral to oral antimicrobials has been shown to have several advantages, including reduction of cannula-related infections, reduction of healthcare costs and possible reduction of discomfort for the patients (Cyriac & James, 2014; Rojas-Reyes & Granados Rugeles, 2006). Information on the de-escalation of antimicrobial therapy was not included in this study.

5.3.3 Indication of antimicrobial treatment

Most of the antimicrobials prescribed were indicated for empiric therapy (83.1%). Prophylactic antimicrobials accounted for 15.2% of the antimicrobials prescribed. Only 1.7% of the antimicrobial prescriptions were indicated for directed therapy. According to the Botswana guidelines, initiating empiric broad-spectrum antimicrobials for moderate to severely ill patients and then subsequently narrowing therapy when microbiological diagnostic test results are available is recommended (Botswana Ministry of Health, 2012). This is consistent with the findings of a point prevalence study carried out in several hospitals in Botswana in 2019, where MDH was one of the hospitals included in the study. The 2019 study reported that culture and sensitivity tests were seldom done, and the majority of antimicrobial therapy was empiric (Paramadhas et al., 2019). Microscopy culture and sensitivity (MC&S) testing is an important aspect of the rational use of antimicrobials as it reduces the risk of treatment failures, and may be helpful in decreasing the emergence of antimicrobial resistance (AMR) (Ansari et al., 2012; Arslan et al., 2017). These tests would potentially increase the incidence of directed therapy with narrow-spectrum antimicrobials, as opposed to the current high incidence of empiric therapy with broad spectrum antimicrobial medicines. Decreasing the unnecessary use of broad-spectrum medicines would be a positive outcome in the efforts to reduce antimicrobial resistance. Delays in obtaining microbiological results from the laboratory was cited as one of the challenges to the selection of antimicrobial therapy by a medical doctor during the semi-structured interviews conducted with staff members.

Doctor: There is delays with culture results uh to sort of show you sensitivities of antimicrobials and I think it's something that we're living within the government hospitals that it doesn't bother us anymore. We just initiate patients on whatever antibiotics you think would benefit them without even considering that.

5.3.4 Duration of antimicrobial treatment

Most of the antimicrobial therapy was given for less than five days (64.7%). It is important to optimise the duration of treatment to ensure long enough exposure of the pathogens to the antimicrobials, while preventing unnecessarily prolonged treatment which could result in increased adverse effects and incidence of AMR (Downes et al., 2014; Gross-Hodge et al., 2020; Tansarli et al., 2019).The results of the study show that the guidelines did not clearly state the recommended duration of therapy for every antimicrobial medicine and infectious

condition. However, based on comparisons made between the results and the recommended durations in the guidelines, results for amoxicillin and amoxicillin-clavulanic acid showed that the majority of prescriptions for those medications were within the recommended duration of therapy range. Results for other antimicrobials such as cefotaxime and metronidazole suggest that the duration of treatment may have been shorter than recommended. This is a concern because the guidelines highlight the need for adequate duration of treatment to avoid treatment failure and the exacerbation of AMR (Botswana Ministry of Health, 2012).

5.3.5 Adherence to prescribing guidelines

For 82.7% of the antimicrobials prescribed, prescribers had complied with the national antimicrobial prescribing guidelines. In 17.3% of the antimicrobial prescriptions, prescribers had deviated from the guidelines. Adherence to the local guidelines, which in this case were the Botswana Antimicrobial Therapy Guide of 2012, in this study was higher than in studies conducted in South Africa and Namibia, where guideline adherence was 45.1% and 62%, respectively (Gasson et al., 2018; Nakwatumbah et al., 2017). The researcher could not find literature stating acceptable parameters for acceptable adherence to antimicrobial prescribing guidelines, however, recommended strategies for AMS include the implementation of measures to improve adherence to antimicrobial prescribing guidelines (Brink et al., 2017; CDC, 2019).

Incidences where the national guidelines were not adhered to include the prescription of gentamicin for a traumatic amputation, where the guidelines recommended cefradine for prophylaxis in orthopaedic interventions, including amputations and open fractures (Botswana Ministry of Health, 2012). Another example was the use of ampicillin and gentamicin for pneumonia treatment where the recommended antimicrobials were either amoxicillin-clavulanic acid, cefuroxime, or cefotaxime.

A study carried out in Botswana showed that prescribers tended to go against prescribing guidelines (Paramadhas et al., 2019). However, this was a multi-centre study, therefore the difference in findings may be due to our study being conducted in the paediatric ward at a single hospital. It is still interesting to note the findings of research done by Paramadhas et al. (2019) in Botswana regarding the adherence to guidelines, as this points to positive outcome in our findings. The difference in results may also be because the Paramadhas study was done on both adults and paediatrics, while our study only included paediatric patients. In a Swedish study by Tell et al. (2015) it was found that prescribers' adherence to national prescribing

guidelines was higher in paediatric patients compared to adults. This might explain why the results of our study, which was focused on paediatric patients, showed higher prescriber adherence to national prescribing guidelines than the multi-centre study.

5.4 Antimicrobial stewardship

A doctor, a nurse and a pharmacist were interviewed to find out what they know about and what their opinions were about the AMS committee at the MDH. They had volunteered to be interviewed and were not necessarily representatives of the hospital. Although it is not possible to generalise based on the interviews of three participants their responses provided insight into the functioning of the AMS committee at the MDH.

The responses of the three participants are provided where appropriate and relevant by using italics. This indicates that it is a direct quote from the interview. Where the responses were inaudible on the voice recordings, this is indicated by three dots "…".

5.4.1 Knowledge of the existence of an AMS committee

Only one of the three HCPs interviewed knew about an existing AMS committee at the hospital, namely the pharmacist. Neither the doctor nor the nurse knew about it. The pharmacist is on the AMS committee, whilst the doctor and nurse interviewed are not. The AMS committee is relatively new. It was established in 2018, and this may account for them not knowing about it yet. On the other hand, it may be due to the reported lack of infrastructure and support for AMS programmes in Botswana, as reported by Paramadhas et al. (2019).

5.4.2 Knowledge of the functioning of the AMS committee

The pharmacist – who is a member of the AMS committee- explained that the AMS committee is a sub-committee of the Drugs and Therapeutics Committee (DTC) at MDH. It reports directly to the DTC at meetings which are held once a month. The AMS committee has a separate meeting prior to the DTC meeting, and the Chairperson of the AMS committee reports their discussions and findings during the DTC meeting.

At the time of the study, according to the pharmacist who was interviewed, the members of the AMS committee and their qualifications were as follows:

- Chairperson of the AMS committee – Medical Doctor
- Secretary – Pharmacist

- Orthopaedic Department representative – Orthopaedic Surgeon
- Paediatric Medical Ward representative – Medical Doctor
- Infection control nurse – Registered Nurse
- Family Nurse Practitioner
- Intensive Care Unit (ICU) representative – Surgeon
- Obstetrics and Gynaecology Department representative – Medical Doctor
- Surgery Department representative – Surgeon
- Laboratory representative – Laboratory Scientist

This seems to be a representative sample of healthcare professionals in the hospital. According to the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology (SHEA) guidelines, the AMS committee should include an infectious control nurse, and should collaborate with medical staff leaders. The composition of this committee thus seems to comply with these guidelines. (Dellit et al., 2007). The guidelines also recommend that the AMS committee should have other members that are not listed here, such as an infectious disease specialist, a clinical pharmacist with infectious disease experience, and a hospital epidemiologist (Dellit et al., 2007). MDH is a district hospital and does not have the capacity to employ all the required specialists.

According to the pharmacist interviewed the AMS committee had not receive any AMS training. From the IDSA guidelines, training of the clinical pharmacist when needed should specific learning needs be identified should be provided (Dellit et al., 2007). The guidelines do not state that training for the other members is required, therefore the AMS committee not having received AMS training at the time of the study was not a negative finding.

The IDSA and SHEA guidelines also state that the expectations of hospital administration of the AMS committee should be set (Dellit et al., 2007). From the results, the roles of the AMS committee members are assigned. For example, the representatives of the different departments are responsible for providing guidance on the use of antimicrobials for their respective departments. The chairperson of the AMS committee is responsible for reporting on AMS to the DTC. The pharmacist explained that the laboratory is responsible for producing a monthly antibiogram report, which should be used to produce guidelines on the use of antimicrobial medicines for the departments in the hospital:

Pharmacist: So, like they are also to produce the guide for the use of antibiotics. For paeds they need to produce a guide for use of antibiotics for all those departments, but we are also

guided by the antibiogram report from the lab. The laboratory produces the antibiogram report on a monthly basis for sensitive microbes, medicines, and all those. So, it's through that report then where the departments can produce a guide on the use of antibiotics, to see which ones are active.

According to Paramadhas et al. (2019) antibiograms assist prescribers in making decisions on antimicrobials but are generally not available in hospitals in Botswana It is fortunate that the laboratory at MDH produces antibiograms, and prescribers should be encouraged to use them to produce guidelines for the prescribing of antimicrobials.

5.4.3 Knowledge of the antimicrobial prescription guidelines, protocols, and Standard Operating Procedures (SOPs) used in the paediatric ward

The participants were asked about the different guidelines, protocols, and SOPs available to them in the paediatric medical ward (PMW) at MDH.

The doctor interviewed mentioned the use of protocols developed at Princess Marina Hospital, which is the largest referral hospital in Botswana:

Doctor: Yes, there are the Botswana General Guidelines, but readily available to the wards we use the one that was made from Princess Marina, [like] the protocols.

The nurse mentioned the use of the Integrated Management of Childhood Illnesses strategy:

Nurse: We have Botswana guideline which is the master one. Then we have 'MCI' guidelines. But specifically, in paediatrics there are specific for certain conditions, for example malnutrition, you have a malnutrition guideline and also TB guidelines. That's what we have.

Paramadhas et al., (2019) reported that guidelines and the current Botswana EML were not always readily available at all hospitals in Botswana. It was interesting to find out that the doctor and the nurse were accessing guidelines other than the Botswana EML which did not seem to be readily available.

5.4.4 Knowledge of policies and programmes in the hospital to control the prescribing of antimicrobials

The doctor (who is relatively new – she's been there for less than a year) described the process of authorisation and protocols that are followed in the PMW at MDH as follows:

Doctor: Only the, with the paediatrician she was the ones who was authorising the antibiotics we were putting a child on. And like I'm saying the protocol book that was devised in Marina which is where we have the school of medicine covers for particular condition, you'd use this and for a particular condition you use this and then there is a dosage as well like for children how much you would use.

This suggests that the prescribers were using the guidelines developed at the Princess Marina Hospital first to find out about the appropriate treatment and dosing, and the paediatrician would then check and authorise the prescription. This follows the rules of good prescribing as outlined by Mol et al. (2004), who emphasised the importance of aligning antimicrobial prescribing practices with the recommended treatment guidelines. According to Objective 4 of the WHO Global Action Plan (GAP) on AMR, adhering to treatment guidelines is in important factor in the fight against AMR (WHO, 2015a).

When asked about the policies and programmes the nurse said that there are different SOPs for different healthcare professionals but not specific ones for antibiotics:

Nurse: I would say we have SOPs. We don't have specific policies for antibiotics. We have SOPs, for example SOPs for prescribing, an example for … and pharmacists. But we don't have specific policies for antibiotics.

5.4.5 Perceived challenges experienced by the AMS committee and prescribers

The doctor mentioned challenges with obtaining results from microbiological tests performed by the laboratory to identify the pathogens present and their antimicrobial sensitivities. The challenges detailed were regarding the time it takes to obtain culture results, which is anything up to 7 days. The doctor stated that because of this delay antimicrobials are initiated empirically. Prescribers try to get a response sooner by contacting the laboratory directly after 48 hours to get a verbal response, but this is not always successful.

Doctor: There is delays with culture results uh to sort of show you sensitivities of antimicrobials and I think it's something that we're living within the government hospitals that it doesn't bother us anymore. We just initiate patients on whatever antibiotics you think would benefit them without even considering that. It's only maybe…most of them come after 7 days and by then the patient would have… and then yes you would call after 48 hours to see if there

has been growth and you can get a verbal "no" there has not been growth but sometimes the recording and the actual conclusions is after seven days.

A study carried out in hospitals in Botswana cited similar concerns, stating that results from culture and sensitivity tests were not always reported in a timely manner (Paramadhas et al., 2019).

The pharmacist mentioned that there was no paediatrician on the AMS committee. There is a paediatrician on the PMW who authorises antimicrobial treatment for paediatric patients before it is administered – as explained by the doctor.

5.4.6 Opinions about the AMS committee

5.4.6.1 Opinions about whether there is a need for an AMS committee at MDH

Neither the doctor nor the nurse knew about the existence of an AMS committee at MDH. However, they both expressed the opinion that the addition of an AMS committee at MDH would be valuable. When asked the question "in your opinion do you think there should be an AMS committee at the hospital?" the responses were as follows:

Doctor: Yes, there should be because that will play a role in audits and stuff to see if patients were given the right antibiotics for a particular condition and sometimes that's because of improper dosing or improper use so that will come in handy.

It is interesting to note that the doctor linked the existence of an AMS committee to having an auditing role. This is indeed one of the functions of an AMS committee and is one of the recommendations made by the CDC as part of its core elements of ASPs (CDC, 2019). The prospective audit and feedback strategy has been found to have positively impacted the prescribing of empirical antibiotics, leading to more appropriate prescribing decisions (Høgli et al., 2016). This method can be implemented by ASPs to assess the use of antimicrobial medications and give feedback to the healthcare professionals to help improve their prescribing practices.

The nurse mentioned another important role of an AMS committee, namely, to monitor the use of antibiotics and the emergence of resistance:

Nurse: Yes, I think we should have. The good part of it, it would help in terms of resistance and monitoring of using those antibiotics.

This is an essential responsibility of the AMS committee. The inappropriate use of antimicrobial medicines has been linked to the development of AMR, therefore one of the functions of the AMS committee is to monitor the use of antimicrobial medications and have interventions in place to reduce the misuse of these medicines (CDC, 2019).

5.4.6.2 Opinions on the functioning and responsibilities of the AMS committee

The pharmacist said that the time spent discussing AMS in the DTC meetings was adequate and seemed satisfied with the structure and function of the AMS committee, considering that it had only been recently formed. The responsibilities of the different members of the committee were defined, as is recommended by the AMS guidelines by IDSA and SHEA (Dellit et al., 2007).

Regarding the role that pharmacists play in AMS at the hospital, the three HCPs interviewed said that pharmacists play an important role in the selection of antimicrobial medicines. According to IDSA guidelines, pharmacists should be trained on infectious diseases to ensure adequate knowledge on the matter (Dellit et al., 2007). It would need to be determined whether the pharmacist has infectious disease training, and if not, this could be a potential area of improvement for the hospital management to consider as part of their support for the AMS committee.

5.5 Study limitations

One limitation of the study is that it did not include all prescriptions of patients admitted to the PMW at MDH during the study period. The patient files included in the study were selected by the researcher only if the diagnosis warranted an antimicrobial medicine prescription. Some prescriptions may have been incorrectly excluded due to human error. Another limitation to the study was the purposive sampling in the qualitative aspect of this research. Some staff in the paediatric medical ward cited time constraints when approached about participating in the semi-structured interviews. The nursing staff also showed some reluctance towards being interviewed. This resulted in only three HCPs being interviewed, which may not have been a representative sample of the medical staff in the paediatric ward at MDH and could have introduced bias to the results of the study. The pharmacist who was interviewed was part of the AMS Committee at MDH, therefore this could have introduced bias into the results.

Retrospective studies can be used in research to analyse exiting data, such as data from patient medical records. Limitations to using this research method exist, and in this study included missing information from patient files, difficulty in comprehending information from the patient files, variations in the level of detail recorded by different medical professionals and difficulty in determining the reasoning for some of the prescribing decisions made by medical doctors. However, this method provided the researcher a relatively inexpensive means to access and study an extensive amount of data and draw reasonable conclusions about certain aspects of antimicrobial prescribing at MDH.

Chapter 6: Conclusion

This research study aimed to investigate the antimicrobial prescribing practices in the paediatric patients at Mahalapye District Hospital (MDH) in Botswana, and to ascertain whether prescribers adhered to national guidelines (the Botswana Antimicrobial Therapy Guide of 2012) when prescribing antimicrobial medicines. The Botswana Antimicrobial Therapy Guide of 2012 were the only guidelines used in this study. The study also aimed to determine whether antimicrobial stewardship (AMS) measures were being implemented at MDH.

The study population for this research was paediatric patients younger than 14 years old who were admitted to the paediatric medical ward (PMW) at MDH and prescribed antimicrobial medicines from January 2018 to December 2018. The study findings suggest that the majority of patients were admitted with community acquired infections, with pneumonia and AGE being the most common diagnoses. These results were consistent with results from paediatric patients in other African countries. Upper respiratory tract infections and bronchiolitis were the third and fourth most common diagnoses. Of all the diagnoses studied, pneumonia was the only disease which showed seasonality. The highest incidence of pneumonia occurred during the winter months in Botswana, which was similar with results from other African countries.

Adherence to the Botswana Antimicrobial Therapy Guide of 2012 was good with respect to the selection of antimicrobial medicines and the duration of treatment. The most prescribed antimicrobials were ampicillin and gentamicin. Their use in combination was not surprising as this is consistent with findings from utilisation studies both in Africa and around the world. The staff who were interviewed indicated that they used prescribing guidelines during their practice at MDH. This might explain the good adherence to antimicrobial guidelines and utilisation of antimicrobial medicines.

The high incidence of empirical prescribing indicates a low reliance on microbiological diagnostic measures for the selection of antimicrobial therapy. During the semi-structured interviews, the medical doctor indicated that delays in obtaining microbiological results from the laboratory resulted in prescribers selecting antimicrobial medicines empirically. According to the pharmacist who was interviewed, the laboratory was responsible for producing a monthly antibiogram report to guide prescribers in their selection of antimicrobial medicines. A

consideration for MDH would be to put measures in place to ensure that laboratory delays are reduced in order to encourage prescribers to utilise microbiological testing to guide their prescribing.

The route of administration for antimicrobial therapy was largely parenteral. Although information on the de-escalation of therapy from parenteral to oral route was not included in this study, this is still a finding that was worth noting as high parenteral use of antimicrobials has been linked to more cannula-related infections, increased healthcare costs and patient discomfort. Use of oral formulations where necessary is recommended. The high reliance on parenteral formulations may be due to severity of illness, young age of patients or the superior bioavailability associated with parenteral administration compared to oral administration of medicines.

According to the pharmacist who was interviewed, the hospital has an AMS committee which had been established in the year prior to the interviews (2018). The committee was a sub-committee of the Drugs and Therapeutics Committee (DTC). The AMS committee members included representatives from the different departments at the hospital, an infection control nurse, and a laboratory representative. This was a positive finding as it showed collaboration with the different hospital departments, which is one of the recommendations from IDSA and SHEA for AMS committees (Dellit et al., 2007). A recommendation regarding the members of the AMS committee is for the inclusion of an infectious disease specialist to co-lead the AMS committee with a clinical pharmacist who has infectious disease experience. Other members that could be included are an information systems specialist and a hospital epidemiologist. Considerations should be made regarding whether there would be a need for additional staff to be hired, or if existing staff could fulfil the duties required. For example, the pharmacist already on the AMS committee could be given specialised infectious disease training if needed, according to recommendations from IDSA and SHEA guidelines (Dellit et al., 2007).

The roles of the AMS committee members were defined, as is recommended by the CDC. The AMS committee members held a monthly meeting to compile a report on AMS, which the chairperson of the committee was responsible for relaying to the DTC. The representatives from each department are responsible for reporting on AMS in their respective departments. They were also responsible for providing guidance on AMS to their departments. This is also a positive finding for MDH as the CDC recommends that hospital management should set expectations for the AMS committee (CDC, 2019). The CDC also outlined the responsibilities

of the AMS committee and these included reporting to hospital management on AMR and AMS at the hospital (CDC, 2019). The manner in which information was communicated from the DTC to the rest of the hospital staff was not explored in the interviews.

The staff who were interviewed had prior knowledge of AMS, with the pharmacist being a member of the AMS committee at the hospital. The doctor linked AMS with the audit process. The nurse mentioned that the AMS committee would have a role in monitoring the use of antimicrobial medicines. these responses reflect an awareness of AMR and AMS measures among the staff who were interviewed and is a positive finding.

The doctor and the nurse who were interviewed did not know of the existence of an AMS committee at the hospital. The CDC outlines the role of management as ensuring that there is awareness of the AMS committee and any ASPs among the staff in the different departments at the hospital (CDC, 2019). This is an area which hospital management could possibly improve. The pharmacist said that he was satisfied with the functioning of the AMS committee. He also felt that the institutional pharmacist played a pivotal role in AMS at the hospital.

In conclusion, this study showed that antimicrobial prescribing guidelines were adhered to in the paediatric ward at MDH. The utilisation of antimicrobial medicines was consistent with what the guidelines recommended and with practices in other African countries. The hospital had an AMS committee in place, and the membership of the committee was largely consistent with recommendations from international guidelines. The roles of the committee were well defined by the hospital management. The staff who were interviewed at MDH were knowledgeable about AMS and that they used prescribing guidelines in their practice. From the results, factors that influenced antimicrobial prescribing in paediatric patients included the various guidelines utilised by prescribing staff at MDH, knowledge of AMR and AMS, and the delays in the availability of laboratory test results.

Recommendations for the hospital would be to improve support of the AMS committee by including more staff according to recommendations in the guidelines, and by ensuring that all departments are aware of the AMS committee and their efforts. The use of microbiological testing as guidance to antimicrobial prescribing is also recommended. The findings of this study may also be reported to the hospital in a formal feedback session.

As the antimicrobial stewardship committee was still in its infancy at the time of the study, recommendations for future studies would be to investigate the nature and success of antimicrobial interventions implemented by the AMS committee at MDH.

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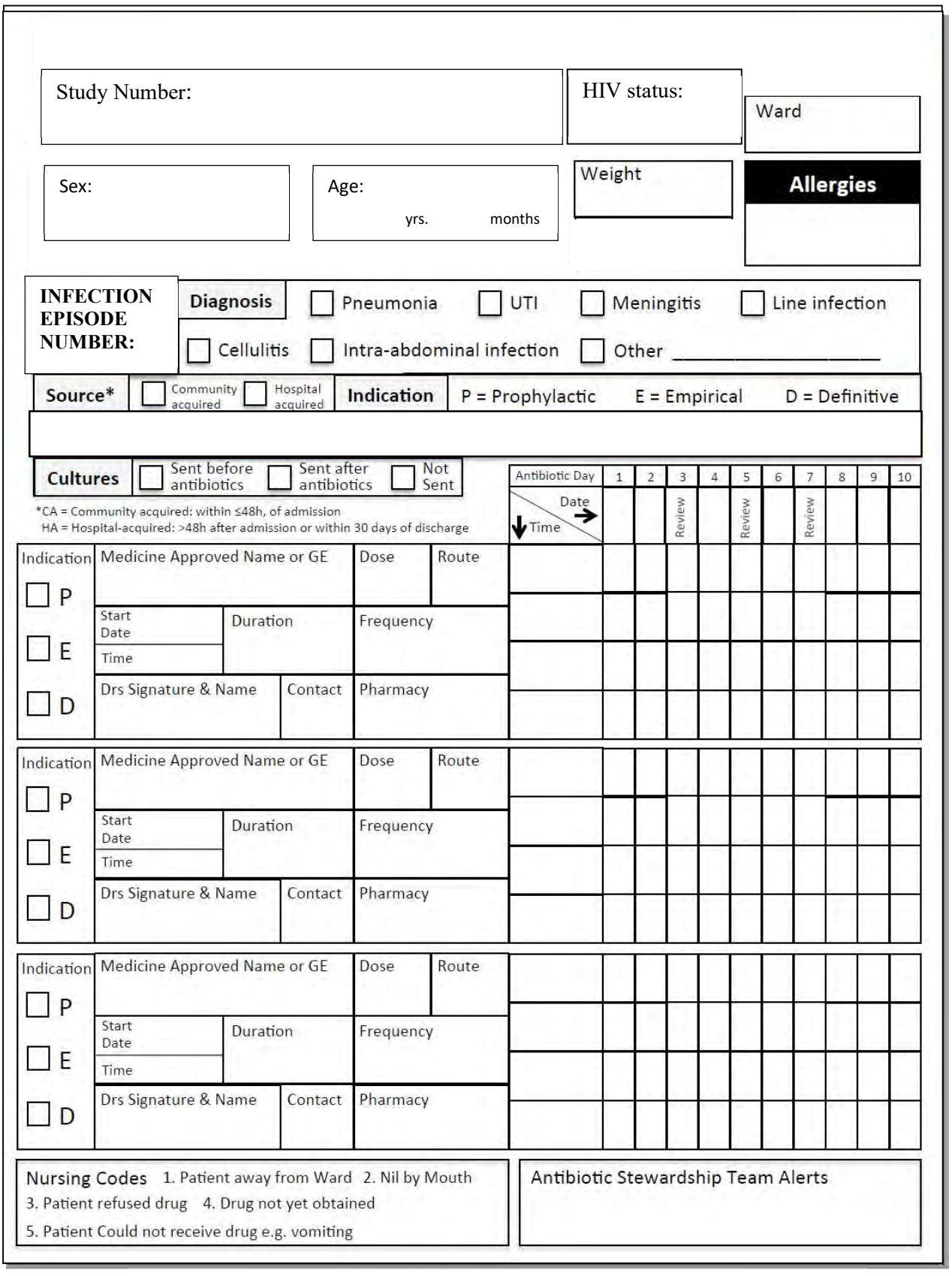
Appendices

Appendix A: Antibiotic Prescription Chart (FIDDSA. 2014)



Study Number:

HIV status:

Ward

Sex:

Age:
yrs. months

Weight

Allergies

INFECTION EPISODE NUMBER:

Diagnosis ☐ Pneumonia ☐ UTI ☐ Meningitis ☐ Line infection
☐ Cellulitis ☐ Intra-abdominal infection ☐ Other _____

Source* ☐ Community acquired ☐ Hospital acquired

Indication P = Prophylactic E = Empirical D = Definitive

Cultures ☐ Sent before antibiotics ☐ Sent after antibiotics ☐ Not Sent

*CA = Community acquired: within ≤48h, of admission
HA = Hospital-acquired: >48h after admission or within 30 days of discharge

Antibiotic Day	1	2	3	4	5	6	7	8	9	10
Date → / Time ↓			Review		Review		Review			

Indication	Medicine Approved Name or GE	Dose	Route
☐ P ☐ E ☐ D	Start Date / Time	Duration	Frequency
	Drs Signature & Name	Contact	Pharmacy

Indication	Medicine Approved Name or GE	Dose	Route
☐ P ☐ E ☐ D	Start Date / Time	Duration	Frequency
	Drs Signature & Name	Contact	Pharmacy

Indication	Medicine Approved Name or GE	Dose	Route
☐ P ☐ E ☐ D	Start Date / Time	Duration	Frequency
	Drs Signature & Name	Contact	Pharmacy

Nursing Codes 1. Patient away from Ward 2. Nil by Mouth
3. Patient refused drug 4. Drug not yet obtained
5. Patient Could not receive drug e.g. vomiting

Antibiotic Stewardship Team Alerts

Once only / Stat dose antibiotics

Indication	Drug	Dose	Route	Date	Time		Time given
☐ P ☐ E ☐ D							
☐ P ☐ E ☐ D							
☐ P ☐ E ☐ D							

Microscopy & Culture results

Date	Site*	Pathogen	Sensitivities

*BC = Blood, MSU = Midstream urine, CSU = Catheter specimen urine, CSF = Cerebrospinal fluid, PS = Pus swab, BM= bone marrow, JA = Joint aspirate, TA = Tracheal aspirate

Appendix B: Permission to use the Antibiotic Prescription Chart

Angella Nyawera <angellar.nyawera@gmail.com>

Antibiotic Prescription Chart

2 messages

Angella R. Nyawera <angellar.nyawera@gmail.com> Mon, Mar 19, 2018 at 9:24 AM

To: marc.mendelson@uct.ac.za

Dear Prof. Mendelson

My name is Angella Nyawera and I am an MPharm student at Rhodes university. I am writing this to request permission to use the Antibiotic Prescription Chart from the FIDSSA website. I would like to apply for ethics approval to conduct a study on the antimicrobial prescribing practices in a hospital in Botswana and would like to use the Antibiotic Prescription Chart as a data collection tool. Please find attached below a copy of my research proposal draft for your perusal.

I look forward to hearing from you.

Kind Regards

Angella Nyawera

Research Proposal- Draft 2.docx

23K

Marc Mendelson <marc.mendelson@uct.ac.za> Fri, Mar 23, 2018 at 1:31 PM

To: "Angella R. Nyawera" <angellar.nyawera@gmail.com>

With pleasure Angella.

Good luck!

Prof Marc Mendelson

President, International Society for Infectious Diseases

Professor of Infectious Diseases

University of Cape Town

Tel +27 21 650 4943

Fax +27 21 650 6184

Twitter @southafricanasp

Marc.mendelson@uct.ac.za

Appendix C: Participant information

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PARTICIPANT INFORMATION DOCUMENT

STUDY TITLE:

Retrospective study on the antimicrobial prescribing practices in paediatric patients in the Mahalapye District Hospital, Central Botswana.

My name is Angella Nyawera and I am conducting this study as part of my Master's degree. The study aims to investigate the antimicrobial prescribing practices in the Mahalapye District Hospital. The objectives of this study are to determine the measures in place to monitor and control the antimicrobial prescribing and use in the hospital, such as the presence of an antimicrobial stewardship committee and programs that have been implemented in this hospital. Semi-structured interviews will be conducted with a representative of the Antimicrobial Stewardship Committee and/or the Pharmaceutical and Therapeutics Committee, pharmacists and medical staff involved in the prescribing and dispensing of antimicrobials. The results obtained from this study will allow us to identify aspects of the antimicrobial stewardship programs that could be broadly adopted or develop interventions that could possibly be implemented in the hospital.

We would like you to consider participating in this study. The next three pages contain information regarding the study. Should you require more information please contact the study researcher or supervisor:

Ms Angella Nyawera	g14n0651@campus.ru.ac.za	+27815377904
Mrs Yolande van Deventer	y.vandeventer@ru.ac.za	+27725752703
Dr Carmen Oltmann	c.oltmann@ru.ac.za	+27466038494

If you require any additional information regarding your rights as a research participant, or if you have complaints regarding this research study, you may contact the Chairperson of the Research Ethics Committee, Faculty of Pharmacy, Rhodes University:

Dr Roman Tandlich	R.Tandlich@ru.ac.za

INFORMATION

You are invited to participate in a research study. This research is being conducted to investigate the antimicrobial prescribing practices in the Mahalapye District Hospital in Botswana. Your participation is voluntary. You have the right to be informed about the study procedures so that you can decide whether you want to consent to participation. This form may contain words that you do not know. Please ask the researcher to explain any words or information that you do not understand.

WHY IS THIS STUDY BEING DONE?

The purpose of this research is to investigate the antimicrobial prescribing practices in the Mahalapye District Hospital.

WHO WILL BE IN THE STUDY?

Interviews will be conducted with the Antimicrobial Stewardship Committee and/or the Pharmaceutical and Therapeutics Committee, pharmacists at the institution as well as other staff involved in prescribing.

WHAT AM I BEING ASKED TO DO?

You will be asked to verbally answer questions asked by the researcher. The interviews will be audio recorded.

HOW LONG WILL THE INTERVIEW LAST?

The interview will take approximately 15-30 minutes to complete. You can stop participating at any time without penalty.

WHAT ARE THE BENEFITS OF BEING IN THE STUDY?

The results of the study will be made available to the hospital. The findings of this research may be used to determine possible interventions which may be implemented at the hospital to strengthen the antimicrobial stewardship program.

WHAT ARE THE RISKS OF BEING IN THE STUDY?

None that we are aware of.

WHAT ARE THE COSTS OF BEING IN THE STUDY?

There is no cost to you.

CONFIDENTIALITY

- No information regarding your participation or responses will be used for any purpose other than to understand the antimicrobial stewardship at the Mahalapye District Hospital.

- Information produced by this study will be stored in the investigator's file and identified by a unique participation number only. The key list connecting your name to specific information about you will be kept in a separate, secure file. Information contained in your records may not be given to anyone unaffiliated with the study in a form that could identify you without your written consent, except as required by law.
- In addition, as audio files will be used in this study you will be asked to give special written permission for their use. You will be given the opportunity to listen to the audio files before you give your permission for their use if you so request. You will also be provided with a copy of the transcript of these audio recordings for verification.
- In accordance with the ethical recommendations of the Health Professions Council of South Africa, audio files of the interviews will be kept in a locked location for six years, or for two years following publication of the study, after which they will be destroyed.

WILL I BE COMPENSATED FOR PARTICIPATING IN THE STUDY?

You will receive no payment for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

- Participation in this study is voluntary. You do not have to participate in this study.
- You may decide to withdraw from the study at any point without penalization.
- A copy of this Informed Consent form will be given to you before you participate in the research.

Appendix D: Consent form

INFORMED CONSENT TO PARTICIPATE IN RESEARCH STUDY

TITLE OF THE STUDY: Retrospective study on the antimicrobial prescribing practices in paediatric patients in the Mahalapye District Hospital, Central Botswana.

PRINCIPAL INVESTIGATOR: Angella Nyawera

SUPERVISORS: Yolande Van Deventer

Carmen Oltmann

I hereby confirm that I have been informed by the researcher, Angella Nyawera, about the nature, conduct, benefits, and risks of the study.

- I have read and understood the above-mentioned information and had the opportunity to consider the information and ask questions, and these have been answered satisfactorily.
- I understand that I will be asked to answer questions regarding the antimicrobial utilization practices at Mahalapye District Hospital. I am aware that this study will involve the audio recording of my interview with the researcher, that the typed transcripts of the audio recorded interviews will not include my name or other identifying information and that I may review the transcripts of the audio recorded interview if I so wish, or at the request of the researcher.
- I understand that my participation is voluntary and that I may, at any stage, without prejudice, withdraw my consent and participation in the study at any time without giving any reason.

PARTICIPANT:

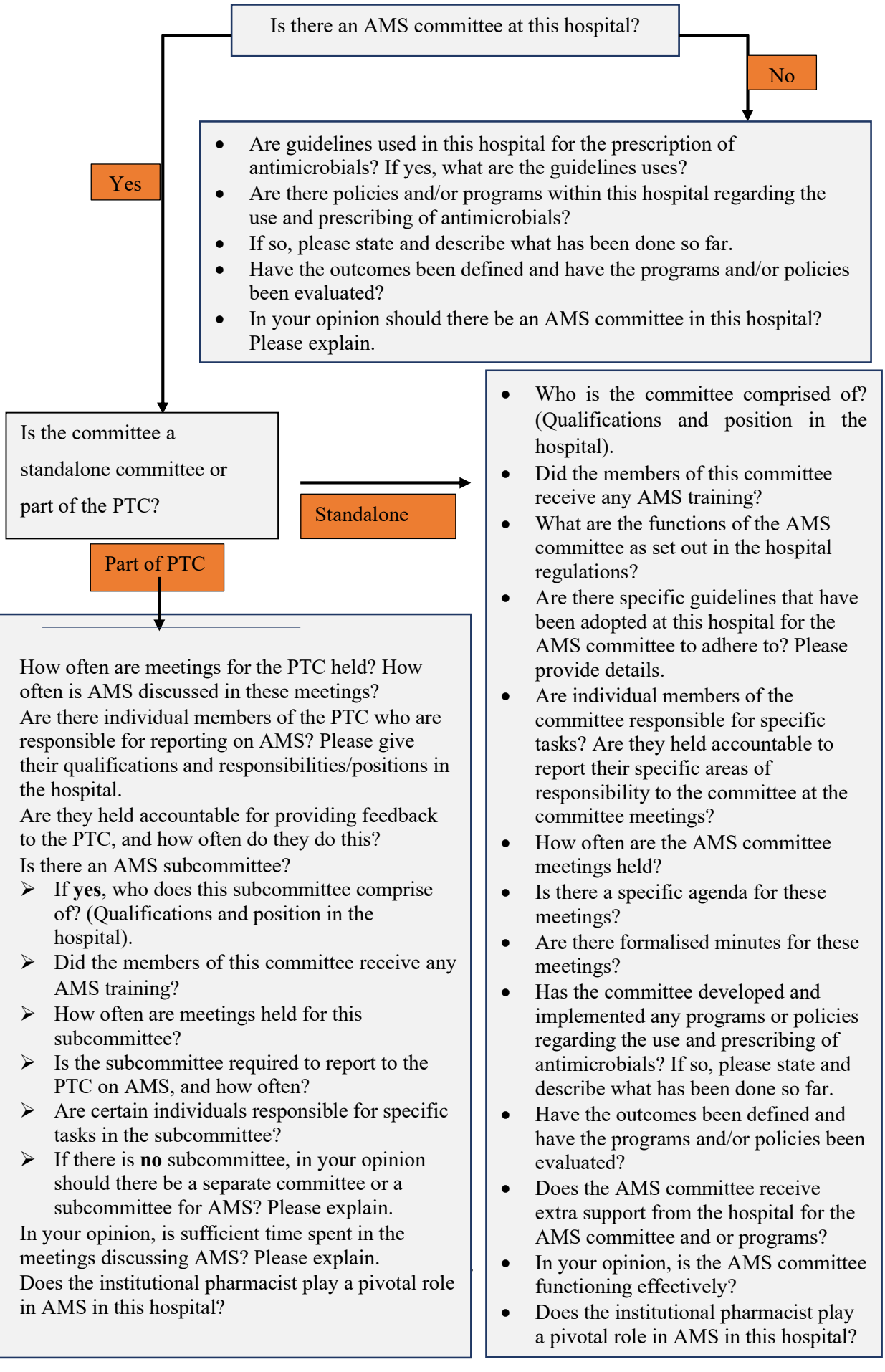
Printed Name Signature Date

I, Angella Nyawera, (researcher) herewith confirm that the above participant has been fully informed about the nature, conduct and risks of the above study.

RESEARCHER:

Printed Name Signature Date

Appendix E: Questions for semi-structured interviews



Appendix F: Ethics approval from the Faculty of Pharmacy Ethics Committee

RHODES UNIVERSITY
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Faculty of Pharmacy
Artillery Road, Grahamstown, 6139, South Africa
PO Box 94, Grahamstown, 6140, South Africa
+27 (0) 46 603 7584
+27 (0) 46 603 7566
www.ru.ac.za

Grahamstown 19th October 2018

From:
Associate Professor Roman Tandlich, PhD
Chairperson of the Faculty of Pharmacy Ethics Committee
Faculty of Pharmacy
Rhodes University
P.O. Box 94
Grahamstown 6140
South Africa
e-mail: r.tandlich@ru.ac.za

To:
Mrs. Yolande VanDeventer Dr. Carment Oltmann and Ms. Angela Nyawera,

Re: Feedback Letter on Ethics Committee Application PHARM-2018-09.

Dear Mrs. Yolande VanDeventer Dr. Carment Oltmann and Ms. Angela Nyawera,

Thank for submitting your application for ethical approval entitled: "Retrospective study on the antimicrobial prescribing practices in paediatric patients in District Hospital, Central Botswana". The revised application was considered by the Faculty of Pharmacy Ethics Committee under the tracking number: PHARM-2018-09. After reviewing the revised application, you have submitted to the Faculty of Pharmacy Ethics Committee, I am happy to inform you the Faculty of Pharmacy Ethics Committee granted conditional approval for your study.

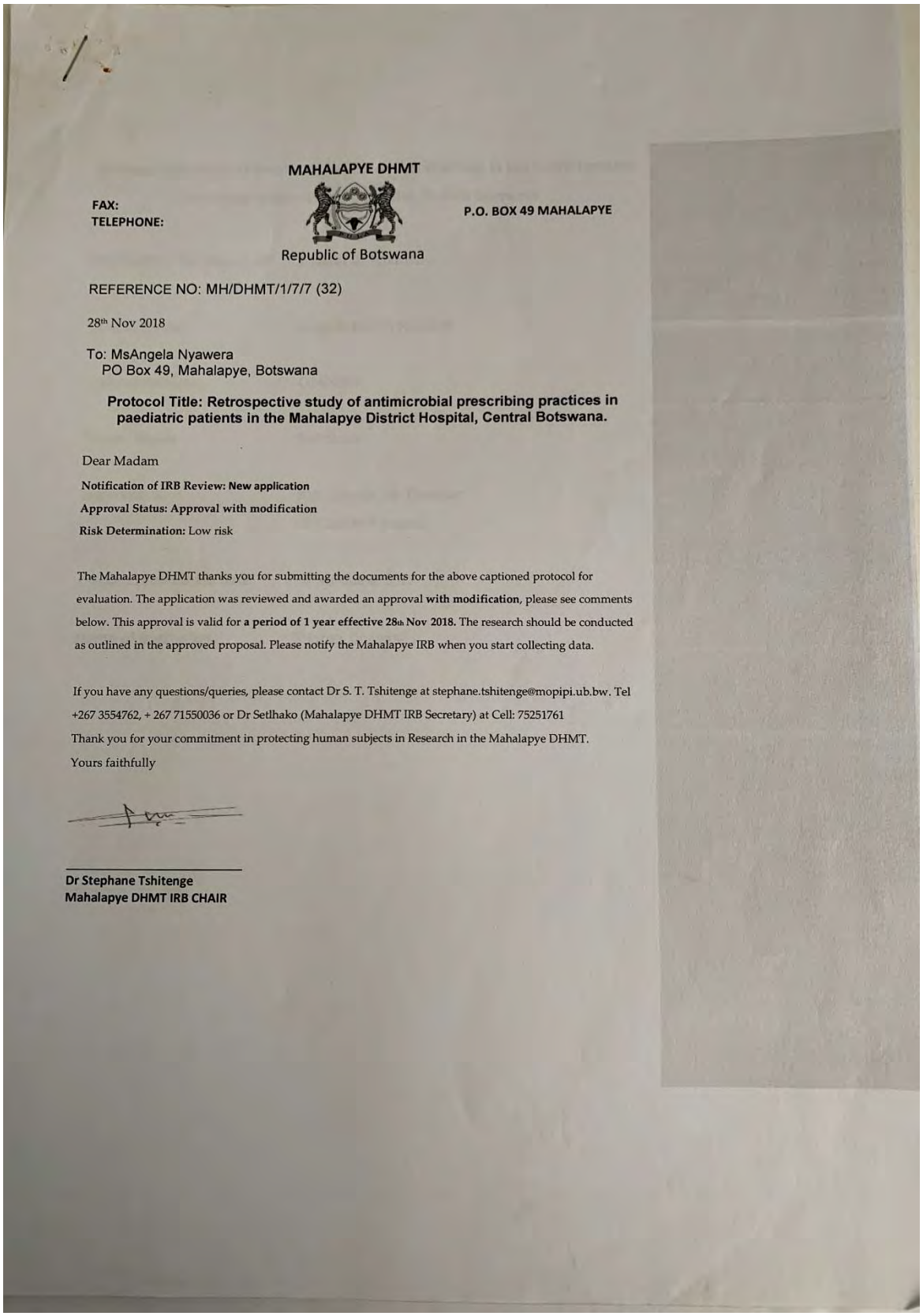
You can proceed to obtain any necessary institutional and/or gatekeeper approval(s). Once these are obtained, please email them to me and the final approval letter will be issued. Please ensure that the Faculty of Pharmacy Ethics Committee is notified should any substantive changes(s) be made, for whatever reason, during the research process.

Yours sincerely,

Roman Tandlich, PhD

CHAIRPERSON: FACULTY OF PHARMACY ETHICS COMMITTEE

Appendix G: Ethics approval from MDH Research and Ethics Board



MAHALAPYE DHMT

FAX:
TELEPHONE:

P.O. BOX 49 MAHALAPYE

Republic of Botswana

REFERENCE NO: MH/DHMT/1/7/7 (32)

28th Nov 2018

To: MsAngela Nyawera
PO Box 49, Mahalapye, Botswana

Protocol Title: Retrospective study of antimicrobial prescribing practices in paediatric patients in the Mahalapye District Hospital, Central Botswana.

Dear Madam

Notification of IRB Review: New application

Approval Status: Approval with modification

Risk Determination: Low risk

The Mahalapye DHMT thanks you for submitting the documents for the above captioned protocol for evaluation. The application was reviewed and awarded an approval **with modification**, please see comments below. This approval is valid for **a period of 1 year effective 28th Nov 2018.** The research should be conducted as outlined in the approved proposal. Please notify the Mahalapye IRB when you start collecting data.

If you have any questions/queries, please contact Dr S. T. Tshitenge at stephane.tshitenge@mopipi.ub.bw. Tel +267 3554762, + 267 71550036 or Dr Setlhako (Mahalapye DHMT IRB Secretary) at Cell: 75251761

Thank you for your commitment in protecting human subjects in Research in the Mahalapye DHMT.

Yours faithfully

Dr Stephane Tshitenge
Mahalapye DHMT IRB CHAIR

Appendix H: Ethics approval from Botswana Ministry of Health

PRIVATE BAG 0038
GABORONE
BOTSWANA
REFERENCE:

REPUBLIC OF BOTSWANA
MINISTRY OF HEALTH AND WELLNESS

TEL: (+267) 363 2500
FAX: (+267) 391 0647
TELEGRAMS: RABONGAKA
TELEX: 2818 CARE BD

REFERENCE NO: HPDME 13/18/1 **13 December 2018**

Health Research and Development Division

Notification of IRB Review: **New application**

Ms Angela Nyawera
P O Box 69
Shoshong

Dear Angela Nyawera

Protocol Title: **RETROSPECTIVE STUDY OF ANTIMICROBIAL PRESCRIBING PRACTICES IN PAEDIATRIC PATIENTS IN THE MAHALAPYE DISTRICT HOSPITAL, CENTRAL BOTSWANA**

HRU Approval Date:	13 December 2018
HRU Expiration Date:	12 December 2019
HRU Review Type:	Expedited Review
HRU Review Determination:	Approved
Risk Determination:	Minimal risk

Thank you for submitting new application for the above referenced protocol. The permission is granted to conduct the study.

This permit does not however give you authority to collect data from the selected sites without prior approval from the management. Consent from the identified individuals should be obtained at all times.

The research should be conducted as outlined in the approved proposal. Any changes to the approved proposal must be submitted to the Health Research and Development Division in the Ministry of Health for consideration and approval.

Furthermore, you are requested to submit at least one hardcopy and an electronic copy of the report to the Health Research, Ministry of Health and Wellness within 3 months of completion of the study. Approval is for academic fulfillment only. Copies should also be submitted to all other relevant authorities.

Continuing Review

In order to continue work on this study (including data analysis) beyond the expiry date, submit a Continuing Review Form for Approval at least three (3) months prior to the protocol's expiration date. The Continuing Review Form can be obtained from the Health Research Division Office (HRDD), Office No. 7A.7 or Ministry of Health website: www.moh.gov.bw or can be requested via e-mail from Mr. Kgomotso Motlhanka, e-mail address: kgmmotlhanka@gov.bw As a courtesy, the HRDD will send you a reminder email about eight (8) weeks before the lapse date, but failure to receive it does not affect your responsibility to submit a timely Continuing Report form

Amendments
During the approval period, if you propose any change to the protocol such as its funding source, recruiting materials, or consent documents, you must seek HRDC approval before implementing it. Please summarize the proposed change and the rationale for it in the amendment form available from the Health Research Division Office (HRDD), Office No. 7A 7 or Ministry of Health website: www.moh.gov.bw or can be requested via e- mail from Mr. Kgomotso Motlhanka, e-mail address: kgmotlhanka@gov.bw . In addition submit three copies of an updated version of your original protocol application showing all proposed changes in bold or "track changes".

Reporting
Other events which must be reported promptly in writing to the HRDC include:
- Suspension or termination of the protocol by you or the grantor
- Unexpected problems involving risk to subjects or others
- Adverse events, including unanticipated or anticipated but severe physical harm to subjects.

If you have any questions please do not hesitate to contact Ms Seeletso Mosweunyane at smosweunyane@gov.bw, Tel +267-3632018 and Mr. K. Motlhanka at kgmmotlhanka@gov.bw, Tel +267-3632751. Thank you for your cooperation and your commitment to the protection of human subjects in research.

Yours sincerely

Ms S. Mosweunyane
for /PERMANENT SECRETARY

MINISTRY OF HEALTH
RESEARCH DIVISION
2018 -12- 13
P/BAG 0038
GABORONE
REPUBLIC OF BOTSWANA