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A RETROSPECTIVE REVIEW ON THE UTILISATION OF MEROPENEM IN A TERTIARY HOSPITAL SETTING

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Masters of Science in Medicine, Clinical Pharmacy.

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Declaration

I, Shameeda Mohun declare that this dissertation is my own unaided work. It is being submitted for the degree of Masters of Science in Medicine (Clinical Pharmacy) at the University of the Witwatersrand, Johannesburg. It has not been submitted for any other degree or examination at any other University.

Shameeda Mohun

05 June 2024

Ethics Declaration

I, Shameeda Mohun, consciously assure that for the research report: A Retrospective Review on the Utilisation of meropenem in a Tertiary Hospital Setting, the following is fulfilled:

1) The presented material is an authentic creation of the author, and it has not been disseminated or featured anywhere else.

2) The paper is not currently being considered for publication elsewhere.

3) The author of the report has presented their own research and analysis honestly and comprehensively.

An official signed plagiarism declaration has been signed (Appendix H). Ethical clearance was received from the National Health Research Database (NHRD) (Appendix E) and the University of the Witwatersrand Human Research Ethics Committee (Medical)(M220537) (Appendix F).

Dedication

This research paper is dedicated to my supportive parents, Abdool Idrisse and Shaheeda Mohun, who encouraged and inspired me throughout the study. Without their love and support, this would not have been possible.

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In completion of this research report, I would like to firstly thank The All Mighty, The All Almighty, The All-Knowing, without Whom, none of this would have been possible.

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Contents

List of Tables

List of Figures

List of abbreviations

AICU	-	Adult Intensive Care Unit
AMS	-	Antimicrobial stewardship
CAP	-	Community acquired pneumonia
CDC	-	Centre for Disease Prevention and Control
CDW	-	Central data warehouse
COVID-19	-	Coronavirus disease
CRE	-	Carbapenem-Resistant Enterobacteriaceae
CRP	-	C-Reactive protein
CT	-	Computed Tomography
CVC	-	Central vascular catheter
DDD	-	Daily defined doses
DHP	-	Dehydropeptise
DUE	-	Drug utilisation evaluation
DOT	-	Duration of therapy
EDL	-	Essential Drug List
ESBL	-	Extended spectrum β-lactamases
EUCAST	-	European Committee on Antimicrobial Testing
HAP	-	Hospital acquired pneumonia
HREC	-	Human Research Ethics Committee
ICU	-	Intensive care unit
IQR	-	Inter quartile range
MDR	-	Multi drug resistant
MIC	-	Minimum inhibitory concentration
NDOH	-	National Department of Health

NHLS - National Health Laboratory Services

NHRD - National Heath and Research Database

NICU - Neonatal Intensive Care Unit

OprD - Outer membrane porin protein D

PCR - Polymerase chain reaction

PCT - Procalcitonin

PD - Pharmacodynamic

PK - Pharmacokinetic

SAASP - South African Antibiotic Stewardship Programme

SAHPRA - South African Health Products Regulatory Authority

SAMF - South African Medicine Formulary

SD - Standard deviation

STG - Standard treatment guidelines

TB - Tuberculosis

TDM - Therapeutic Drug Monitoring

UN - United Nations

WHO - World Health Organisation

List of appendices:

Abstract

Introduction: The discovery of antibiotics is widely regarded as a groundbreaking accomplishment in the medical industry, as it has facilitated the elimination of countless diseases. Nonetheless, the overuse and reckless consumption of these medicines have led to a global upsurge in antibiotic resistance, particularly in broad-spectrum antibiotics such as meropenem, which are often prescribed for severe infections.

Aim: The aim was, therefore, to assess the utilisation trends of meropenem in treating patients at a tertiary hospital located in the North-West Province of South Africa.

Methodology: This study involved a retrospective review of hospital records at a 396-bed tertiary hospital in the public sector of South Africa, for patients who were prescribed meropenem between January and December 2021. A total of 218 patient files were included in the analysis after removing the duplicates and incomplete files. Variables investigated were patient demographics, prescribing criteria, diagnosis, treatment indication, microorganisms, and sensitivity cultures, as well as the appropriateness of prescribing. Descriptive statistics were employed to analyse the data.

Results: Meropenem was primarily used empirically in adult patients (65.1%), while clinicians treating paediatric patients generally reserved its use for definitive cases (55.1%). Recording of the source of infection was poor with 72.1% of adults and 96.6% of paediatrics lacking such documentation. Although all prescriptions analysed were deemed valid, only a small percentage of treatments were considered appropriate (3.1% in adults). The study also revealed that clinicians frequently ordered microbiological cultures and blood sensitivity tests prior to administering antibiotics, at rates of 50.4% in adults and 71.9% in paediatrics. Notably, the most cultured bacteria were *Klebsiella pneumoniae* (25.2%) in paediatric patients and *Acinetobacter* species (25.0%) in adults.

Conclusion: The study's results reveal a clear contrast between suggested protocols and clinical practices in the real world, stressing the pressing need for effective antimicrobial strategies to counter the growing threat of meropenem resistance. Several areas of concern were identified, including non-adherence to guidelines, insufficient step-down therapy, and incomplete documentation. Despite being a broad-spectrum antibiotic intended for definitive diagnoses, meropenem is often prescribed empirically, further highlighting the need for continuous medical education, practical therapeutic committees, and frequent drug utilisation evaluations to tackle this issue.

SYNOPSIS OF REPORT

Chapter One of this dissertation provides a background to the study. It delves into the historical context of antibiotics, the development of antibiotic resistance and the associated risks. A summary of the aims and objectives are included in this chapter.

Chapter Two provides a comprehensive literature review which draws attention to the utilisation of meropenem in a tertiary setting. It sheds light on the various applications of meropenem, its present uses, and the elements responsible for the development of antibiotic resistance against it. It examines the current strategies aimed at curtailing the spread of antibiotic resistance and importance of such.

Chapter Three of this dissertation provides a summary of the methodology and study design.

Chapter Four includes the results of the study. These are presented through tables or graphs, with separate analysis for adult and paediatric patients. The chapter focuses on various aspects of meropenem use, including diagnosis, indication, and treatment duration, as well as microbiological trends.

Chapter Five of the dissertation analyses the results from the chapter above. This section offers a comprehensive evaluation of the current patterns derived from the outcomes.

Chapter Six of this dissertation outlines the future recommendations, strengths, limitations and conclusion of the study.

CHAPTER 1: INTRODUCTION

This chapter is constructed to review the consequences of irrational antibiotic use and the imminent threat of antibiotic resistance. It emphasises the factors that have resulted in the global rise of antibiotic resistance. This chapter comprises of an overview of the problem statement and the importance of antimicrobial stewardship and includes the research question, objective and aim of the study.

1.1 Background

One of the greatest medical breakthroughs of the 20th century has been the introduction of antibiotics with the discovery of penicillin in 1928 initiating a period of drug innovation and implementation in both animal and human health (Hutchings *et al.,* 2019). Prior to the discovery of penicillin, infections such tuberculosis (TB), syphilis, the plague, and cholera had reached epidemic proportions and throughout history claimed the lives of many people (Mohr *et al*., 2016). Antibiotics have revolutionised the treatment of these diseases and made many novel medical procedures such as chemotherapy, organ transplant and open-heart surgery possible (Hutchings *et al.,* 2019).

The period from the 1940s to the 1980s is commonly referred to as the 'golden age' of antibiotics due to the annual discovery of new antibiotics. This era witnessed the discovery of several classes of antibiotics including aminoglycosides, tetracyclines, amphenicols, polypeptides, penicillin, sulfones, salicylates, macrolides, glycopeptides, polymyxins, nitrofurantoin, lincosamides and cephalosporins amongst others (Hutchings *et al.,*2019).

As the number of available antibiotics increased, so did their use. Antibiotics are viewed as a safe, effective, relatively inexpensive and short-term form of therapy (Bonten and Lowbury., 2022). However, this 'golden age' was short lived as the world began to face infections caused by bacteria that were no longer susceptible to conventional antibiotics (Bonten and Lowbury., 2022).

Antibiotic resistance is defined by the Centre for Disease Prevention and Control (CDC) as the ability of bacteria to resist the therapeutic effects of antibiotics. Resistance can develop through several mechanisms which can be categorised as phenotypic (growth patterns) or genotypic (presence and/or expression of genes) mechanisms which allow bacteria to overcome the antimicrobial activity of antibiotics (Davison *et al*., 2000).

Antibiotic resistance is rapidly rising to dangerous levels globally and affects all countries regardless of economic status (Basetti *et al*., 2021). The World Health Organisation (WHO) declared antibiotic resistance as one of the major global threats facing humanity. It is estimated that globally antimicrobial resistant infections are responsible for over 700 000 deaths annually and should appropriate measures fail to be implemented, the number of deaths is expected to increase to about 10 million annually by the year 2050 (Siachalinga and Mufwambi, 2022). Antibiotic resistance is complex and there are several factors contributing to its acceleration, including:

- Excessive prescription of antibiotics promoting its irrational use;
- Misuse of antibiotics in the agricultural sector**;**
- Inadequate infection control in health care settings**;**
- Overall poor standards of cleanliness and sanitation due to environmental and economic factors**;**
- Inadequate pharmacovigilance systems;
- Lack of essential diagnostic equipment and resources leading to delay in diagnosis or errors in treatment;
- Absence of new antibiotic discovery due to reduced research and development.

Bacterial infections have become increasingly difficult to treat due to the growing capability of bacteria to develop, acquire, and spread resistant mechanisms. This trend has led to a continuously expanding list of infections that are becoming more challenging to manage, including but not limited to pneumonia, tuberculosis, and gonorrhoea. Evidence of this phenomenon was observed in a clinical trial that was prematurely terminated in 2004, as participants were infected with strains of bacteria that had developed resistance to the antimicrobial drug under investigation, highlighting the urgency of the situation (Charles and Grayson, 2004).

Multi-drug resistant (MDR) bacteria are a type of antimicrobial resistant bacteria that have been discovered across the globe. These bacteria exhibit diverse patterns of resistance to multiple antibiotics, posing a significant challenge for effective treatment. Magiorakos *et al*., (2012) has defined MDR bacteria as bacteria which have, "*acquired non-susceptibility to at least one agent in three or more antimicrobial categories*". A few of the MDR bacterial strains, now have limited treatment options. Bacteria which have begun to exhibit MDR characteristics include gram-positive bacteria such as Vancomycin-resistant *enterococci;* Methicillin-resistant coagulase-negative *staphylococci***;** Methicillin-resistant *Staphylococcus aureus***;** Multidrug-resistant *Mycobacterium tuberculosis* and *Mycobacterium avium* complex**.** Gram-negative MDR bacteria include *Acinetobacter baumannii; Pseudomonas aeruginosa; Stenotrophomonas maltophilia* and *Klebsiella pneumoniae* (Charles and Grayson, 2004).

Such MDR infections were commonly found in hospitalised and critically ill patients. The types of infections often lead to higher medical costs, extended hospital stays and ultimately an increased mortality rate. In many cases, even last resort antibiotics are no longer a viable option for treatment (Frieri *et al*., 2017). These types of MDR infections cause a drastic increase in mortality and morbidity rates (Khameneh *et al*., 2016).

Meropenem, a bactericidal antibiotic belonging to the carbapenem class, has shown to be effective in treating multi-drug resistant (MDR) pathogens in both adults and children. The antibiotic primarily works by inhibiting bacterial wall synthesis, and its broad-spectrum activity makes it an ideal treatment option for severe infections such as hospital and community-acquired pneumonia, septicaemia, and bacterial meningitis. These findings have been supported by Baldwin *et al*. (2008) and Steffens *et al*. (2021).

However, meropenem resistance is increasing with the increased (inappropriate) use of the drug (Mahini *et al*., 2013). Resistance is especially prominent among gram-negative pathogens. Acinetobacter species and *Pseudomonas aeruginosa* has demonstrated resistant patterns recently to many carbapenems and while meropenem is still active against these pathogens, it may not be for much longer (Al-Hadithi *et al*., 2020; Arias and Murray., 2022).

1.2 Problem Statement

To assist in combatting the rise of antibiotic resistance, many hospitals implemented antimicrobial stewardship (AMS) programs. The programs play an essential role in optimising the appropriate use of antibiotics with the goal of reducing the occurrence of resistance, enhancing patient safety and therapeutic outcomes, and reducing the overall hospital and patient costs (MacDougall and Polk., 2005).

Antimicrobial stewardship (AMS) programs are founded on the principle of understanding the relationship between antibiotic usage and resistance. In the prevention of antimicrobial resistance, these programs play a crucial role as part of a multifaceted approach. They are carried out through a collaborative effort that involves policies, management programs, strategies, and protocols to ensure the proper management of currently available antibiotics. In order to ensure effective stewardship, it is imperative to choose the right drug and use it in the correct dosage and for the appropriate duration. This helps in curing infections while keeping toxicity to a minimum and also reduces the likelihood of the development of resistant bacterial strains. To evaluate and improve medication prescribing, administration, and rational use, AMS programs often include antimicrobial drug utilization evaluation (DUE) studies. The World Health Organization (WHO) has identified DUE studies as a means of:

i. defining the appropriate medicine use,
ii. auditing the prescribing criteria,
iii. providing feedback on identified problems to the prescribers and,
iv. monitoring of stipulated criteria.

By performing a DUE study on meropenem use in a public hospital, prescribing patterns can be evaluated (Mahini *et al.,*2013).

1.3 Dispensing in the public institution

Meropenem is subject to strict regulation at select public sector hospitals due to two primary reasons. Firstly, the aim is to promote the judicious use of the antibiotic to prevent the emergence of resistance. Secondly, the high cost of meropenem necessitates its careful usage.

Various protocols have been established to regulate the prescribing and dispensing of meropenem (Appendix A) The dispensing process typically employed by most public sector hospitals is depicted in Figure 1.

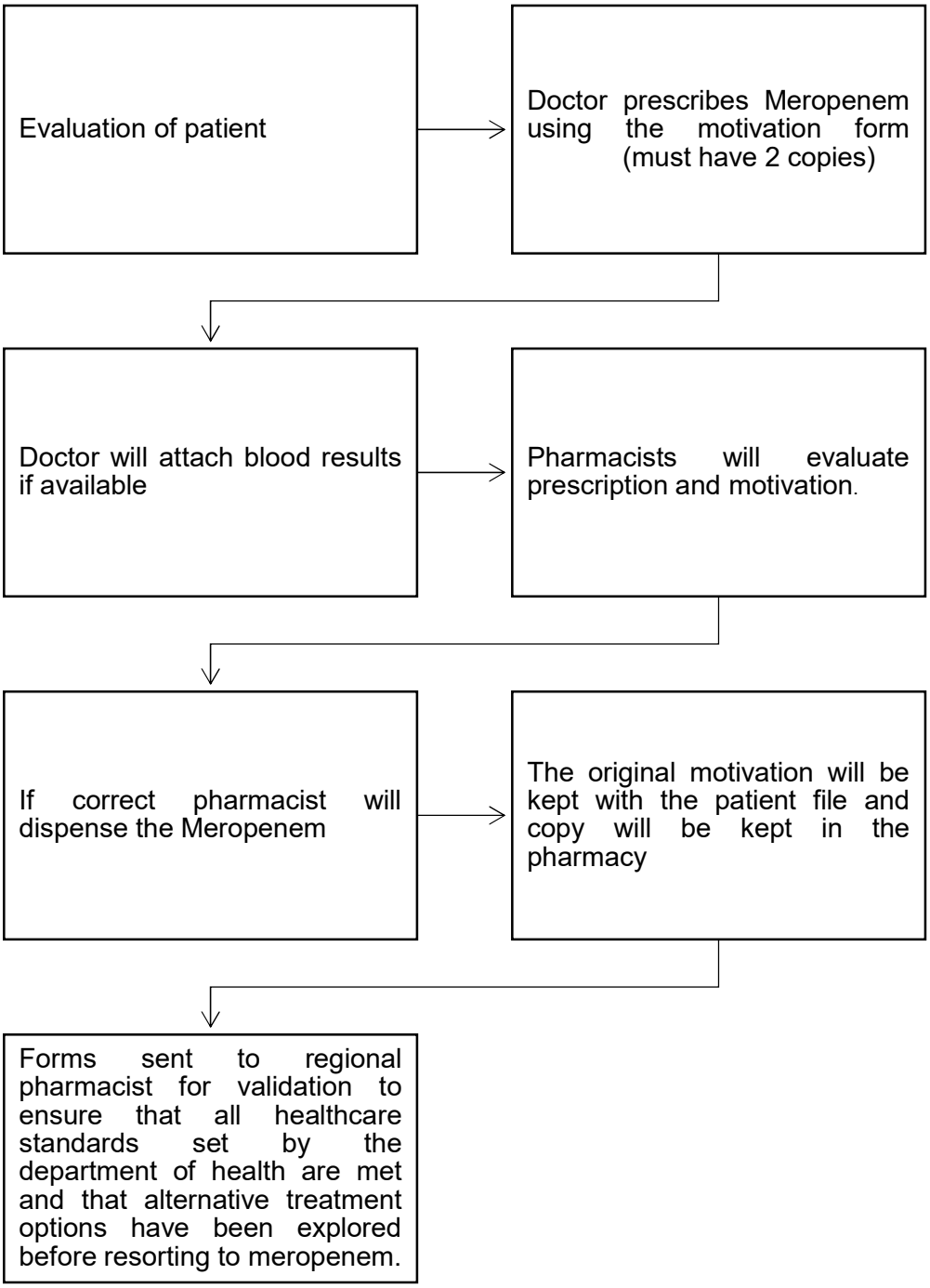

Figure 1. Schematic illustration of standard operating procedure of the dispensing process of meropenem at most tertiary public institutions in South Africa.

Medical officers in the public sector are required to fill out the "Application for Non-Formulary Item per Patient" form (Appendix B); commonly referred to as the motivation form; prior to prescribing meropenem to their patients. This form serves to encourage the responsible use of antibiotics by providing pertinent patient details and validating the necessity for the prescription. Additionally, the forms are considered in the allocation of the hospital's budget for the upcoming fiscal year.

1.4 Aim

This study aimed to assess the utilisation of meropenem in treating patients at a tertiary hospital located in the North-West Province of South Africa, through the retrospective review of patient records from January 2021 to December 2021.

1.5 Objectives

- To investigate the demographic profiles of hospitalised patients who were prescribed and administered meropenem.
- To evaluate the practical application of meropenem in accordance with patient clinical findings.
- To assess the appropriateness of meropenem use (prescribing patterns), against the benchmark Essential Drug List (EDL) and Standard Treatment Guidelines (STG) guidelines for public hospital use of meropenem.

1.6 Summary

The introduction of antibiotics has been one of the greatest medical breakthroughs in history.Antibiotics have been a safe and effective form of infectious disease treatments; however, they have also succumbed to overprescribing and irrational prescribing in the clinical setting. As a result, there has been a global increase in antibiotic resistance. Meropenem, which is a broad-spectrum antibiotic, often used in the case of severe infection has also started exhibiting signs of resistance. To combat this, many hospitals have introduced antibiotic stewardship programs to help curb the rise in antibiotic resistance. Therefore, through evaluating the appropriateness of meropenem use in a tertiary, public hospital in the North-West Province of South Africa, this study aimed to provide valuable findings on rational meropenem utilisation in the study setting. Thus, the objectives of this study included investigating the demographic profiles of hospitalised patients receiving

meropenem and the practical application thereof in relation to patient clinical findings, with the final objective of assessing meropenem use for appropriateness in relation to benchmark clinical guidelines in the public healthcare sector.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

This chapter is a narrative literature review that focuses on the specific applications of meropenem in a tertiary public institution. This chapter further highlights the prevalence of antibiotic resistance with respect to meropenem, including its mechanisms of resistance, and underscores the significance of antimicrobial stewardship in addressing this issue.

2.2 Prevalence of antimicrobial resistance

The escalating prevalence of antibiotic resistance is posing a serious challenge to the efficacy of existing antibiotics and their recommended therapeutic regimens. The issue is multifaceted as it is affecting all sectors including social, economic, medical, and anthropogenic sectors (Ahmad and Khan, 2019).

A study conducted by Aslam *et al.* (2018) has brought to light the concerning prevalence of MDR bacteria, commonly associated with hospital-acquired infections. Shockingly, it is estimated that these bacteria are responsible for approximately 99,000 deaths annually in the United States alone. In 2006, reports indicated that hospital-acquired pneumonia and sepsis caused around 50,000 deaths and cost the American economy an estimated $8 billion. Renowned organizations and institutions, such as the CDC, the Infectious Diseases Society of America, the World Economic Forum, and WHO, have recognized the escalating prevalence of antibiotic resistance as a global public health concern (Aslam *et al.,* 2018).

According to Aslam *et al.* (2018), antibiotic resistance has made a significant impact on the global population. If this trend continues, it is predicted that around 444 million individuals may succumb to MDR infectious diseases by 2050, posing a severe threat to public health. The study emphasizes the need for immediate action to be taken to address this issue and prevent further harm to human health.

Many African countries face a dearth of data on antibiotic resistance intensity. A recent report by Siachalinga *et al.* (2021) indicated that only 14.9% of these nations have a national policy for infection prevention and control, while a meagre 4.3% possess a national plan to tackle antimicrobial resistance. Alarmingly, just three countries in the region have reported

having an antimicrobial stewardship program (Siachalinga *et al.,* 2021). These low figures are the result of inadequate quality-assured microbiology labs in the area and the limited attention given to antimicrobial resistance compared to other public health concerns (Porter *et al.,* 2021). However, despite these obstacles, significant progress has been made in researching and implementing interventions to combat antimicrobial resistance in Africa (Siachalinga *et al.,* 2021).

2.3 Importance of antimicrobial stewardship

The National Department of Health (NDOH) in South Africa has recognized the pressing issue of antimicrobial resistance and has taken action by developing the National Antimicrobial Resistance Strategy Framework (Chetty *et al.,* 2022). In recent years, South Africa has seen a significant increase in the prevalence of gram-negative bacteria that produce extended-spectrum beta-lactamase (ESBL) and carbapenem-resistant Enterobacteriaceae (CRE). According to Boyles *et al.* (2017), the cost of antibiotics alone for a tertiary hospital in the Western Cape was R 2 191 594.00 in 2011. Even more concerning, von Pressentin *et al.* (2019) reported that only 45.1% of primary health care facilities in Cape Town adhered to national guidelines. South Africa, like other African countries, faces various challenges, including limited expertise and resources for infectious diseases and the uneven distribution of public institutions (Brink *et al.,* 2016).

The goal of antibiotic stewardship is to optimise and ensure the control of antimicrobial treatment administered in both in hospitalised patients and the out-patient setting. Further goals include the assurance of cost-effective medication, enhance patient outcomes, and limit the rise of bacterial resistance (Luyt *et al.,* 2014). As such, many hospitals have introduced antimicrobial stewardship programs to help promote the rational use of antibiotics.

Antimicrobial stewardship (AMS) programs are implemented to encourage appropriate antibiotic use and prevent the development of antimicrobial resistance. Hospitals typically adopt two organizational approaches for AMS programs: restrictive strategies that involve pre-prescription authorizations, and enabling strategies that involve post-prescription review and feedback (Vincentini *et al.,* 2022). In a study conducted in Italy between 2017 and 2019, Vincentini *et al*. compared the effectiveness of these two models and evaluated the overall

impact of AMS programs in reducing antimicrobial resistance. The study revealed that during the study period, antimicrobial usage decreased by 4%, while the rates of antimicrobial resistance decreased by 16% for methicillin-resistant *Staphylococcus aureus* (MRSA) and 23% for carbapenem-resistant enterobacteria. The results also showed that both models were equally effective in reducing antimicrobial resistance (Vincentini *et al.,* 2022).

Álvarez-Lerma *et al.* (2018) conducted a study at a general hospital in Barcelona to evaluate the efficacy of an antimicrobial stewardship program in critical care. The study analysed a total of 5002 patients, 1971 patients' pre-intervention and 3031 patients' post-intervention. The study results demonstrated that prior to intervention, 88.6% of patients received more than one antimicrobial agent, while after implementation of the program, this decreased to 77.2% (Álvarez-Lerma *et al.,* 2018).

Additionally, the mean daily defined doses (DDDs) of all antimicrobials used in the intensive care units (ICU) decreased from 246.8 to 192.3 per 1000 patient days. The study also demonstrated a decrease in the use of cephalosporins, quinolones, and glycopeptides. The ICU stay ratios decreased from 178.9 to 148.6, and days of therapy (DOT) decreased from 66.7 to 54.60 days. Therefore, the results of the study indicated that implementing an AMS program in a single ward, such as the ICU, for a period of five years leads to a notable reduction in the usage of antimicrobials (Álvarez-Lerma *et al.,* 2018).

Katz *et al*. conducted a meta-analysis of 22 in 2021 that examined antibiotic usage in Neonatal ICU units within the United States of America. The study focused on the differences in neonates compared to older children regarding antibiotic exposure, drug metabolism, and infection identification and diagnosis markers. The results showed that while blood cultures remain the gold standard for diagnosis, an increasing number of clinicians rely on biomarkers like C-Reactive protein (CRP) and procalcitonin (PCT) to aid in diagnosis. Compared to the gold standard blood culture, CRP had a sensitivity of 62% and a specificity of 74% for detecting late onset sepsis in neonates. However, using CRP alone was not effective as 152 cases of late onset sepsis were missed and 156 were erroneously diagnosed. Another study analysed by Katz *et al.* (2021), conducted in Europe with over 1700 infants enrolled indicated that physicians who followed the PCT protocol had a 10-hour

decrease in antibiotic therapy without any difference in reinfection or death. The study's conclusion suggests that adhering to AMS programs can decrease the use of antibiotics without any detrimental clinical outcomes in this high-risk population (Katz *et al.,* 2021).

Antimicrobial stewardship programs face significant challenges in both public and private hospitals throughout South Africa. The lack of infectious disease expertise and resources represents a major obstacle, along with the difficulty posed by the geographical distribution of institutions, particularly in large hospital networks (Brink *et al.,* 2016).

In a study conducted by Brink *et al*. AMS programs were implemented in 47 private hospitals across South Africa. The program utilised an adapted version of the Institute for Healthcare Improvement Model and the Breakthrough Series Collaborative approach. The interventions were centred on reducing the unnecessary and inappropriate use of antibiotics, such as avoiding cultures that were not required before the commencement of empirical antibiotics, limiting the antibiotic treatment duration to 7 or 14 days, refraining from using multiple antibiotics concurrently and prohibiting the simultaneous use of double or redundant antibiotics (Brink *et al.,* 2016).

According to the research conducted by Brink *et al*. none of the hospitals surveyed had established local antibiotic policies or guidelines, nor did they have any antimicrobial stewardship program committees in place. These findings align with a more recent study conducted by Chetty *et al.* in 2022, which aimed to assess the current state of antimicrobial stewardship activities in public sector hospitals in Kwa-Zulu Natal province, South Africa. The study revealed that although 75% of public-sector hospital facilities in the province had established antimicrobial stewardship program committees, very few of them met regularly. Specifically, only one facility held bi-monthly AMS meetings, while less than 30% convened monthly and less than a quarter met every four months (Chetty *et al.,* 2022).

Brink *et al.* revealed that the implementation of antimicrobial stewardship programs resulted in a significant decrease in overall DDD per 100 patient days from 95% to 83% and a 19.6% drop in overall antibiotic consumption. Additionally, Messina *et al.* conducted a study in 2015 where an antimicrobial stewardship program was implemented in 33 private sector hospitals in South Africa, focusing on compliance with intravenous antimicrobial administration within

one hour. The study showed that initially, only 14.5% of patients received antibiotics, but after the program's implementation, the number increased to 78.4% of patients (Messina *et al*., 2015).

According to both studies, healthcare establishments without expertise in infectious diseases can reap substantial benefits from pharmacist-led antimicrobial stewardship programs. By concentrating on fundamental interventions, specialised pharmacists can significantly enhance the prompt delivery of antimicrobials (Brink *et al*., 2016 and Messina *et al.,* 2015).

The effectiveness of AMS programs hinges on factors such as psychological, organisational, and cultural dynamics. The successful implementation of these programs in day-to-day clinical practice, with the support of hospital pharmacy personnel, is of utmost importance as the use of these programs to facilitate appropriate and restrained antimicrobial treatment can have a significant impact on the well-being of all patients (Álvarez-Lerma *et al.,* 2018).

2.4 Importance of drug utilisation evaluation studies

The WHO defines rational drug use as the provision the appropriate medication in the correct dosage and for the necessary duration specific to the patient. To encourage this practice, drug utilisation evaluation (DUE) studies play a vital role in AMS programs. By evaluating medication prescription and administration, DUE studies aid in determining the appropriateness of drug usage.

The concept of a DUE was coined in the 1960s by Arthur Engel and Pieter Siderius when the need to compare drug use in different countries and regions was identified. These studies provide insight into the patterns of drug use, which in turn will inform healthcare professionals and pharmacovigilance teams about signs of irrational drug use. Through careful analysis of generated patterns, it is possible to develop and implement effective policies and guidelines aimed at halting the progression of such cases. As demonstrated in Figure 2, which is adapted from the 2003 WHO publication Introduction to Drug Utilisation Research, Drug Utilisation Evaluation (DUE) can be a valuable tool for informing policy reform and guiding the development of rational prescribing guidelines. Thus, such studies are considered a suitable tool for the monitoring of antibiotics such as meropenem in a hospital setting.

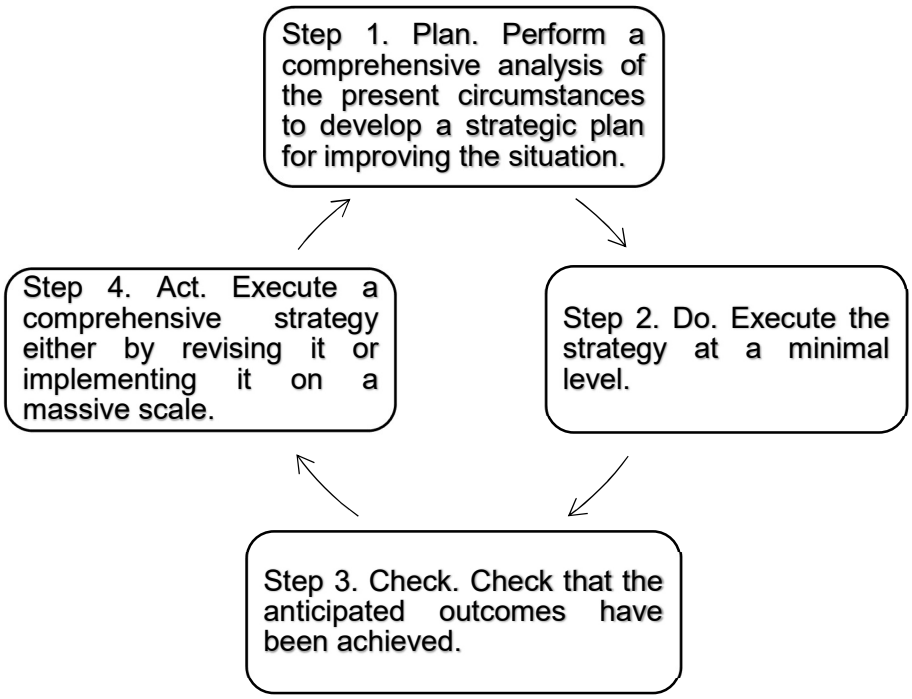

Figure 2. Schematic illustration of the quality control cycle of a DUE study adapted from Introduction to drug utilisation research (WHO, 2003).

2.5 Meropenem: indications and advantages of use

Carbapenems are broad-spectrum, bactericidal antibiotics, that inhibit the bacterial cell wax synthesis process, thereby hindering bacterial growth and proliferation (Steffens *et al.,* 2021).

Meropenem exhibits *in vitro* activity against majority of the clinically significant aerobes and anaerobes such staphylococci, enterococci, *Pseudomonas aeruginosa*, Enterobacteriaceae and *Haemophilus influenzae* (Baldwin *et al.,* 2008). In addition, meropenem also exhibits low host toxicity at therapeutic doses, which makes it ideal for treating infections among multiple patient groups (Steffens *et al.,* 2021).

Meropenem is one of the few highly effective antibiotics for treating MDR bacteria in adults and children. Its broad-spectrum activity against both gram-negative and gram-positive bacteria makes it a valuable treatment option. The drug's effectiveness is directly related to the amount of time its concentration exceeds the minimum inhibitory concentration (MIC) at

the site of infection meaning that the longer its concentration remains above MIC, the greater the chance of therapeutic success. With its low protein binding of approximately 2%, nearly all of the drug remains pharmacologically active (Steffens *et al.,* 2021). Due to the spectrum of activity meropenem is an optimal option for addressing numerous severe infections such as hospital and community-acquired pneumonia, septicaemia, bacterial meningitis, complicated intra-abdominal infections, febrile neutropenia, complicated skin and skin structure infections, complicated urinary tract infections, obstetric and gynaecological infections, and pulmonary infections, particularly in individuals with cystic fibrosis (Baldwin *et al.,* 2008).

Meropenem, like other antibiotics in its class, is not easily deactivated by most β-lactamases (β-lactamases are enzymes produced by bacteria that have been found to provide multi-resistance to a variety of beta-lactam antibiotics, such as penicillins, cephalosporins and monobactams). Additionally, it can be administered as either a bolus dose or infusion (Baldwin *et al*., 2008). Meropenem is considered more suitable than imipenem for the treatment of infections in patients with renal insufficiency due to its stability in the presence of the renal enzyme dehydropeptidase (DHP)-1. Unlike imipenem, which is susceptible to deactivation by the DHP-1 enzyme and necessitates co-administration with cilastatin, meropenem does not require an additional compound for stability. Furthermore, meropenem is associated with a lower incidence of nausea and vomiting, rendering it well-tolerated and conducive to patient compliance (Baldwin *et al.,* 2008).

Meropenem is a hydrophilic molecule that exhibits exceptional tissue penetration, including the lung, skin, interstitial fluid, peritoneal fluid, intra-abdominal tissues and cerebrospinal fluid (CSF), following intravenous administration. Its limited propensity makes it an optimal choice for the management of bacterial meningitis, distinguishing it from other carbapenems (Baldwin *et al*., 2008; Steffens *et al*., 2021).

2.6 Meropenem and its effect on hospital acquired infections

Majority of nosocomial infections are caused by pathogens that can elude the antimicrobial effects of biocidal agents. These pathogens include six highly virulent and resistant strains, namely Enterococcus faecium, *Staphylococcus aureus, Klebsiella pneumoniae,*

Acinetobacter baumannii, Pseudomonas aeruginosa, and *Enterobacter spp*. Collectively, they are referred to as the ESKAPE pathogens (Mulani *et al.,* 2019).

Over time, antibiotics are becoming less effective against ESKAPE pathogens. Since 2010, the Clinical and Laboratory Standards Institute (CLSI) guidelines for recommended antibiotics have undergone significant changes for ESKAPE pathogens (Mulani *et al.,* 2019). In 2019, the European Committee on Antimicrobial Testing (EUCAST) released the 10th version of the breakpoint table, which analyses the cut off points and technical issues for antimicrobial in vitro susceptibility test (Diaz et al., 2022). The minimum inhibitory concentration (MIC) is a crucial clinical cut off point that considers the clinical formulation, dosage, pharmacokinetic and pharmacodynamic rules and behaviors. It distinguishes between treatable and non-treatable microorganisms that are susceptible or not susceptible to the antimicrobial, enabling doctors to make informed treatment decisions (Diaz et al., 2022).

As suggested by Munting et al. (2022), this change in the EUCAST criteria could be associated with an increase of meropenem prescriptions particularly for the treatment of *Pseudomonas aeruginosa.* According to a recent investigation by Munting et al. (2022), an excessive use of meropenem was identified as a consequence of switching from empirical therapy to meropenem following susceptibility testing outcomes. This highlights the urgent requirement for antibiotic stewardship interventions (Munting et al., 2022).

Staphylococcus aureus has become increasingly resistant to meropenem, leading to its removal from the guidelines. Despite this, meropenem remains effective against *Klebsiella pneumonia, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter spp*, as reported by Mulani *et al.* in 2019.

According to a study by Ramsamy *et al.* (2018), which examined the trends of ESKAPE pathogens in South Africa's KwaZulu-Natal province over five years, carbapenem resistance rose from 4% in 2014 to 16% in 2015. The study found particularly high rates of resistance in *Klebsiella pneumoniae* and *Acinetobacter baumannii*.

Similarly, in another study carried out at a hospital in Indonesia in 2021, researchers Dahesihdew and Fanani found that the effectiveness of meropenem in treating ESKAPE infections had decreased from 72% in 2019 to 68% in 2020. However, after implementing antimicrobial stewardship (AMS) policies and programs, the effectiveness of meropenem in

treating ESKAPE infections rose to 84% in 2021. This highlights the positive impact of AMS in combating antibiotic resistance and improving patient outcomes.

2.7 Rise in resistance against meropenem

Similar to other antibiotics, the rise in clinical usage of meropenem has led to an increase in resistance (Mahini *et al*., 2013). In 2010, a study conducted by Wang *et al.* involved the collection of 3892 isolates from teaching hospitals across China. The study aimed to determine the minimum inhibitory concentrations (MIC) of 11 antimicrobial agents using the agar dilution method. The researchers discovered that the susceptibility of *Pseudomonas aeruginosa* remained stable between 2003 and 2008, but there was a significant decrease in susceptibility of *Acinetobacter* spp. (from 94.6% to 60.7%). These findings align with those of Rhomberg *et al.* in 2009, which indicated that the susceptibility of *Pseudomonas aeruginosa* was at 85.4% and *Acinetobacter* spp. was at 45.7%.

Resistance is especially prominent among gram-negative pathogens. Acinetobacter species and *Pseudomonas aeruginosa* has demonstrated resistant patterns recently to many carbapenems and while meropenem is still active against these pathogens, it may not be for much longer (Al-Hadithi *et al*., 2020; Arias and Murray, 2022).

Resistance mechanisms in bacteria can be categorized into two main types: intrinsic resistance and acquired resistance. Intrinsic resistance refers to the inherent structural or functional properties of bacteria that allow them to resist the effects of specific antibiotics. On the other hand, acquired resistance is a result of the acquisition of resistance genes through horizontal gene transfer or mutation. These mechanisms of resistance continue to evolve, with new transmission vectors being discovered regularly (Aslam *et al*., 2018).

In the last 20 years, the emergence of β-lactamases like carbapenemases, metallo-β-lactamases, and extended-spectrum β-lactamases (ESBLs) has caused a rise in acquired MDR infections, leading to carbapenem resistance (Aslam et al., 2018). This is further evidenced by a 2011 study by *Riera et al.,* which demonstrated that inactivation of outer membrane porin protein D (OprD), a substrate-specific outer membrane porin in bacteria such as *Pseudomonas aeruginosa*, increased the MIC of meropenem. Additional

mechanisms, such as AmpC (chromosomal cephalosporinase) or efflux pump overexpression, were also found to contribute to this issue (*Riera et al.,* 2011).

It is essential to limit the use of meropenem due to the potential negative impact of its irrational use. The World Health Organization has categorized meropenem as a Watch group antibiotic, highlighting the importance of monitoring and prioritizing it for AMS programs (Pauwels *et al*., 2021). While meropenem is a versatile and well-tolerated drug, overuse can result in increased drug expenditure, drug resistance, poor therapeutic outcomes, and longer hospital stays. Therefore, it is crucial to preserve and regulate the use of meropenem to prevent these adverse consequences (Aslam *et al*., 2018).

2.8 Meropenem and its effect on hospital acquired infections

Majority of nosocomial infections are caused by pathogens that can elude the antimicrobial effects of biocidal agents. These pathogens include six highly virulent and resistant strains, namely Enterococcus faecium, *Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter spp*. Collectively, they are referred to as the ESKAPE pathogens (Mulani *et al.,* 2019).

Over time, antibiotics are becoming less effective against ESKAPE pathogens. Since 2010, the Clinical and Laboratory Standards Institute (CLSI) guidelines for recommended antibiotics have undergone significant changes for ESKAPE pathogens (Mulani *et al.,* 2019). In 2019, the European Committee on Antimicrobial Testing (EUCAST) released the 10th version of the breakpoint table, which analyses the cut off points and technical issues for antimicrobial in vitro susceptibility test (Diaz *et al.,* 2022). The minimum inhibitory concentration (MIC) is a crucial clinical cut off point that considers the clinical formulation, dosage, pharmacokinetic and pharmacodynamic rules and behaviors. It distinguishes between treatable and non-treatable microorganisms that are susceptible or not susceptible to the antimicrobial, enabling doctors to make informed treatment decisions (Diaz *et al*., 2022).

As suggested by Munting et al. (2022), this change in the EUCAST criteria could be associated with an increase of meropenem prescriptions particularly for the treatment of *Pseudomonas aeruginosa.* According to a recent investigation by Munting et al. (2022), an excessive use of meropenem was identified because of switching from empirical therapy to

meropenem following susceptibility testing outcomes. This highlights the urgent requirement for antibiotic stewardship interventions (Munting et al., 2022).

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2.8.1 Antibiotic challenges during the COVID-19 pandemic

In December 2019, the SARS-CoV-2 virus was first identified in Wuhan, China, and it is responsible for the coronavirus disease 2019 (COVID-19). The WHO proclaimed COVID-19 a pandemic on March 11, 2020, and the virus has since spread aggressively throughout the world (Dlewati *et al*., 2021).

COVID-19 predominantly manifests as a respiratory illness, displaying symptoms similar to those of pneumonia. This resemblance complicates clinical assessment, often resulting in the empirical use of antibiotics (Nestler *et al.,* 2020 and Al-Hadidi *et al.,* 2021). Meropenem has demonstrated efficacy in treating pneumonia by exhibiting activity against pathogens such as *H. influenzae*, *Enterobacter* spp., *Klebsiella* spp., and *Pseudomonas* spp., all of which are recognised as causative agents of hospital-acquired pneumonia (HAP) (Baldwin *et al.,* 2008).

During the COVID-19 pandemic, therapeutic approaches often relied on pre-existing treatments adapted to the pathogenesis of COVID-19. While bacterial co-infection is a common occurrence in viral infections, there remains a significant knowledge gap

concerning co-infection in COVID-19 patients (Yulia *et al.,* 2022). Consequently, physicians frequently resorted to prescribing a broad spectrum of antimicrobials despite the viral origin of COVID-19 and the limited evidence of bacterial superinfection in most cases. This challenge was exacerbated by the absence of specific antiviral treatments or vaccines for COVID-19, complicating the differentiation between bacterial pneumonia and COVID-19 (Diewati *et al.,* 2021).

Meropenem continues to serve as the first-line therapeutic option for managing intensive care unit (ICU) patients afflicted by multidrug-resistant (MDR) gram-negative pathogens. However, its administration often hinges on the clinical judgment of prescribers. Evidence suggests that the extensive use of antibiotics during the COVID-19 pandemic may precipitate the proliferation of multidrug-resistant bacteria (Yulia *et al.,* 2022).

2.9 Diagnosis of infection

In critically ill patients, infections frequently occur, and timeous and effective management can be challenging due to delayed diagnosis, difficulties in identifying causative microorganisms and the prevalence of MDR strains. However early identification of the causative agent, followed with the appropriate therapy is associated with improved outcomes (Vincent *et al*., 2016).

The clinical indications of infection, such as fever and raised white blood cell count, are not specific and can be found in various other conditions as such diagnosis of infection still requires culture-based techniques, which can take several days to yield results. Standard tests for infection diagnosis involve a range of technologies, including microbial cultures, polymerase chain reaction (PCR) assays, and antigen binding assays (Vincent *et al*., 2016). The study of bacterial culture is crucial for investigating virulence, antibiotic susceptibility, and genome sequence, all of which contribute to our understanding and treatment of diseases (Lagier *et al.,* 2015). Rapid culture results allow for the accurate selection of antibiotics, ultimately leading to shorter hospital stays, reduced expenses, and more efficient therapy.

Wang *et al.* noted that *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella* species, *Enterobacter* species, *Acinetobacter* species, *Proteus* species, *Citrobacter* species, and *Serratia* species are the most cultured bacteria in hospitals. However, the antimicrobial susceptibility of these organisms is constantly changing. Over the course of the study, Wang

et al. found that the prevalence of multidrug resistance, especially in *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, has significantly increased. Previously susceptible to antibiotics like cefotaxime and ceftriaxone, these organisms are now only susceptible to a limited number of antimicrobials due to high usage leading to an increase in MDR isolates.

As such the delay in receiving microbiological culture results and the increasing prevalence of antimicrobial resistance, there is a growing trend towards the "right first time" approach when making therapeutic decisions. To support this approach, the South African STG and South African Medicines Formulary (SAMF) provide prescribing guidance. Both resources recommend the use of meropenem as an empirical treatment for serious infections and multidrug-resistant pathogens (Table 1 and 2). As a result, meropenem has become a widely used and specialized antibiotic in South Africa.

Table 1: Protocol for meropenem prescribing summarised from National Hospital Standard Treatment Guidelines for Adults, 2019

Condition	**Description**	**Meropenem dosage for adults**
Febrile Neutropenia	Meropenem indicated only if fever develops after 48hours after admission	1 g 8 hourly IVI
Hospital Acquired Pneumonia (HAP)	HAP with prior intravenous antibiotic use within 90 days.	2 g 8 hourly IVI
Meningococcal meningitis	Indicated for patients with severe penicillin allergy and confirmed meningococcal disease	2 g 8 hourly IVI for 7 days
Pneumococcal meningitis	Indicated for patients with severe allergy to penicillin	2 g 8 hourly IVI for 10 days.
Haemophilus influenza	Indicated for patients with severe allergy to penicillin	2 g 8 hourly IVI for 10 days.

Table 2: General prescribing protocol for Paediatric patients (SAMF 13th edition)

Condition	**Dosage in Paediatrics**
In severe infection	IV Infusion over 5 to 30 minutes, 20-40mg/kg/dose 8 hourly, max 2 g Over 50kg – same as adults
Meningitis	40mg/kg 8 hourly IVI

2.10 Utilisation trends of meropenem

Meropenem is an antibiotic that has been the subject of numerous DUE studies due to its significance. A literature review conducted by Steffens *et al*. (2021) explored the use and therapeutic drug monitoring (TDM) of meropenem. The study analysed 35 studies from different parts of the world to determine the pattern of meropenem usage. The results showed that 85.71% of the patients who received meropenem were critically ill patients admitted to the ICU, diagnosed with sepsis or septic shock. The majority of the patients were adult males over the age of 57. The predominant diagnoses included lung infections, urinary tract infections, intra-abdominal infections, and bloodstream infections, which align with the indications for meropenem as outlined in the National Standard Treatment Guidelines (STG) of South Africa. The study also revealed that the bacterial strains most frequently involved were *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* (Steffens *et al.,* 2021).

The studies on intravenous meropenem administration show that the dosage ranges from 1g to 2g every six, eight, or twelve hours, which adds up to 3g to 6g per day. For patients with severe infections or bacteria with higher MIC, meropenem infusions are either continuous or prolonged. Critically ill patients receive prolonged infusion to maintain a higher concentration of the drug in the blood plasma for a longer period. These findings prove that the South African national STG guidelines align with that of international standards (Steffens *et al.,*2021).

Steffens *et al*. (2021) findings are consistent with Basu *et al*. (2022) studying utilization trends in low-income countries in Africa, Asia, and Latin America. These countries experience a high prevalence of multidrug-resistant bacterial infections due to the overuse of broad-spectrum antibiotics in hospitals. Antibacterial resistance is exacerbated by antibiotic shortages, particularly in African countries such as Kenya, Mauritius, and Ethiopia, as well as limited laboratory resources, poor microbiological symptoms, and inadequate communication of results.

According to Steffens *et al*. (2021), 57% of the studies suggest an antibiotic stewardship program, such as therapeutic drug monitoring (TDM), as a useful practice. Critical illness can cause pathophysiological changes in the body's functions, affecting the distribution and clearance of meropenem and ultimately impacting its plasma levels. This makes it difficult for current empirical regimens to provide adequate coverage. By analysing antibiotic use, we can prevent prolonged use and limit the emergence of antibiotic resistance (Basu *et al.,* 2022).

2.11 Summary

Meropenem is a broad-spectrum restricted antibiotic which is effective against both gram-positive and gram-negative antibiotics. This makes a primary choice for the treatment of various infections such as pneumonia and sepsis. However, over the past two decades, there has been a decrease in susceptibility to meropenem due to antibiotic resistance. Antibiotic resistance has been classified as a global issue by WHO and CDC. One way to combat the rise in antibiotic resistance and preserve the use of this restricted antibiotics is to perform a DUE study. The methodology section, which is the next chapter, details the methods and procedures utilized in this study.

CHAPTER 3: METHODOLOGY

3.1 Introduction

This chapter presents the approach utilized in this study, encompassing the study's structure, sampling methods, data origins, data collection tools, and data analysis. Furthermore, the justification of the procedure and collection procedure will be discussed.

3.2 Study design

This study was a quantitative retrospective review of patient records. The patient records of hospitalised patients that were prescribed meropenem were reviewed during the period of January 2021 to December 2021.

In 2021, the prevalence of COVID-19 was still a major concern, however vaccination campaigns were gradually initiated throughout the year. The purpose of choosing this year was to analyse the utilisation patterns of meropenem throughout the year. As such data was collected for the period of January 2021 to December 2021.

3.3 Study site

The study took place at a tertiary level hospital in the North-West province of South Africa. This hospital was chosen due to its status as one of three tertiary healthcare facilities in the province, as well as being the largest public sector hospital in the district, boasting a total of 396 beds. With an array of medical, surgical, obstetric, psychiatric, and emergency services available, it caters to one of the largest metropolitan areas in the North West province and holds the important role of being the primary referral hospital within the district.

All wards in the hospital were included for analysis. For the purpose of this study, the hospital wards were divided into the following categories:

1. Intensive care units (adult)
2. Intensive care units (paediatric)
3. General medical wards (adults)
4. General medical wards (paediatric)
5. Obstetrics and gynaecology ward

6. Psychiatric wards
7. Casualty (emergency services)

3.3.1 Distribution of meropenem

Like many other hospitals in the public sector, the study site employs the process depicted in Figure 1. Additionally, the site maintains a set of prerequisites that must accompany any application for non-formulary items, such as blood sensitivity findings and prior treatment and diagnosis. This policy is available for review in Appendix A.

3.4 Study Population

The study population included the patient records of all hospitalised paediatric and adult patients who were prescribed and administered meropenem during the study period. Records of patients that met the following inclusion criteria were considered for inclusion from the study population.

3.4.1 Inclusion criteria

- All ages
- Male and female patients
- Hospitalised during the study period January – December 2021.
- Only patient records that indicated meropenem being prescribed and administered were included. This included both meropenem naïve and reinitiated patients.

For any medication to be dispensed a valid prescription must be provided. A valid prescription is issued for legitimate medical purpose by a legal practitioner. In this study the validity of the prescription was measured against the following criteria (as seen in Appendix C)

- Valid as per requirements stated in the Medicines and Related Substances Act 101 of 1965
- Date
- Patient name and details
- Prescriber name and details

- Prescription validated by pharmacist.

Using the criteria above, 287 prescriptions were analysed of which only 218 prescriptions were found to be valid.

3.4.2 Exclusion criteria

- Lost or incomplete patient non-formulary item application (motivational forms) which included:
    - Motivational forms which have not been signed by both medical officer and pharmacist.
    - Motivational forms not signed by medical officer and validated by pharmacist. These applications are denied, and the medical officer is requested to complete a new application.

3.5 Sampling

The study utilised pharmacy data obtained from the patient's non-formulary applications (Appendix E) which is submitted by the medical officer to the pharmacy. As per the Standard Operating Procedures (SOP) of the hospital, all applications are required to be kept for a minimum of six years (National Health Act No. 61 of 2003). The data was analysed to identify patients who had been prescribed and administered meropenem during the study period, resulting in 287 patients being identified. The inclusion and exclusion criteria were applied to these prescriptions and corresponding forms, and after the selection process, only 218 patient forms were found to be eligible, this is illustrated in Figure 3 below. No further sampling methods were employed since the total number of eligible patients were included in the study.

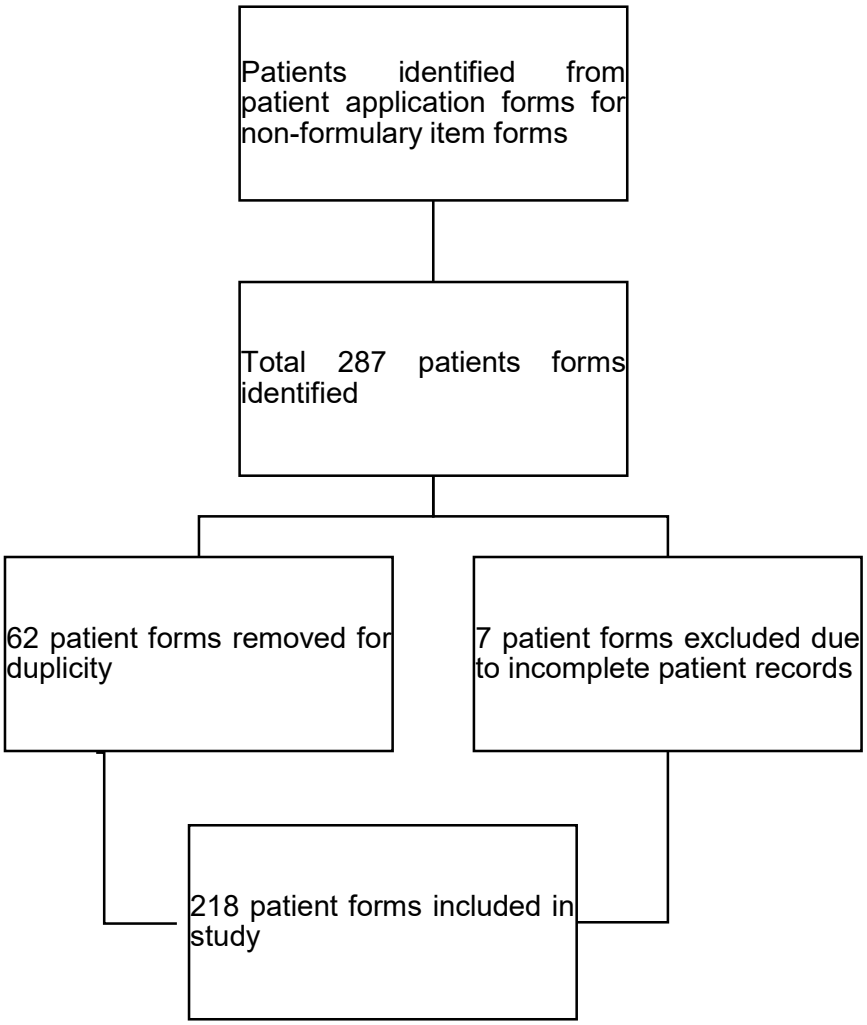

Figure 3. Schematic diagram illustrating the identification and selection process of patient forms.

3.6 Data sources and collection

The patient application form for non-formulary items per patient (Appendix B), also known as the motivation forms, is a crucial component of the patient record and must accompany the patient file when being submitted to pharmacy. Once reviewed the original from will be kept in the pharmacy and a copy filed in the patient file. These forms are subjected to the same Standard Operating Procedure (SOP) of patient record filing and must be kept for a minimum of five years. The forms contain vital information such as patient demographics, diagnosis, prescribed antibiotic details (including name, strength, dose and duration), current

and/or previous treatment and the reason for treatment failure, as well as information on blood culture tests of antimicrobial susceptibility.

To maintain confidentiality, this information is transcribed onto the general data collection tool (Appendix D). This tool is modified from the South African Antibiotic Stewardship Programme (SAASP). In cases where laboratory test results are missing, the National Health Laboratory Services (NHLS) central data warehouse (CDW) system can be used to retrieve the missing data using the patient hospital number. The NHLS CDW number is a database where all blood cultures requested by prescribers are archived.

Records are reviewed both electronically and physically to ensure no data is overlooked. Where data was missing on the patient forms, patient files were reviewed.

3.7 Appropriateness of prescribing

Assessing the appropriateness of clinical drug usage involves a thorough review of drug selection, drug indication, drug interaction, dosage, route of administration, and contraindications. This evaluation process helps identify existing or potential issues and allows for the development and implementation of interventions aimed at promoting the appropriate use of clinical drugs (Bian *et al*., 2021).

The appropriateness of the prescription was assessed by adhering to the requirements specified in the Good Pharmacy Practice (GPP) guidelines and the general prescribing protocols outlined by the National Hospital Standard Treatment Guidelines (STG) and the South African Medicines Formulary (SAMF). The guidelines presented in the STG, specifically outlined in Table 1 and 2, were utilised as the benchmark for evaluating the appropriateness of the prescription.

The appropriateness assessment was conducted by the principal investigator in accordance with the above-mentioned guidelines and protocols. Data was gathered utilising a standardised tool as detailed in Appendix E.

3.8 Data analysis

The data collected was captured onto Microsoft Excel® and was subsequently processed for analysis. The data cleaning process involved rectifying inconsistent data entries,

removing duplicate records, and screening for errors that may have resulted from data transfer.

Descriptive statistics was conducted on the data set using both Microsoft excel and STATA-® 17.0 Edition. Descriptive statistics including mean and median with standard deviations were calculated.

The variables that were collected and documented for each patient can be seen in Table 3 below:

Table 3: Description of variables

Variables	**Description**
Study number	Allocated by the researcher to maintain confidentiality
Demographics	Age and gender
Prescribing criteria	This includes the name, strength, dose, route of administration and frequency of the prescribed antibiotics
Diagnosis	Diagnosis of the patient as indicated on the non-formulary application.
Indication	Indication of treatment to ascertain if it is prophylactic, empiric or definitive.
Source of infection	Indication of the origin of infection to ascertain if it is community-acquired (infection detected within 48 hours), hospital-acquired (infection not present or in incubation at the time of admission) or of an unknown origin.
Microorganisms and sensitivities cultured	To ascertain sensitivity patterns of isolated microorganisms

Microbiological data was obtained from the NHLS CDW database, and microbiological sensitivity tests were requested by the prescriber. Blood cultures were subjected to automated culture tests at the NHLS, yielding results that included the type of microorganism cultured and its susceptibility to various antibiotics. Notably, access to results was limited to meropenem only from the CDW.

3.9 Ethical Consideration

Authorisation to access patient files was granted by the National Health and Research Database (NHRD) for this study (Appendix F). Ethical approval was obtained for the Human Research Ethics Committee (HREC(Medical) of the University of the Witwatersrand was granted (M220537) (Appendix G). Since this was a retrospective analysis of patient data, no informed patient consent was required for the viewing of patient data.

The patient information was safeguarded in compliance with the regulations outlined in the Personal Protection of Information Act of 2013, as well as the guidelines delineated in the Declaration of Helsinki. All data was collected using the general data collection tool (Appendix D). Patient names and dates of birth were not recorded to ensure anonymity, and each patient was allocated a study number. Additionally, clinician details were not recorded. All recorded data was kept confidential and only made available to the principal investigator. The motivation forms were not removed from the hospital and stored in secured cupboard within the pharmacy premises, the data was electronically transferred onto a password-protected device.

The list of study numbers and electronic data was saved in a password-protected file and was kept in accordance with hospital SOP for five years. This information was accessible to the primary investigator, supervisors, and ethics committee if necessary.

There was no known risks or direct benefits to the patients for participating in the study. The dignity and wellbeing of the patients was always protected and all information was treated with the strictest confidence.

CHAPTER 4: RESULTS

4.1 Introduction

This chapter examines the findings of the study performed. This chapter will address the following findings: files excluded/missing files, patient demographics, the utilisation of meropenem, microbiological cultures, validity of prescription and appropriateness of treatment.

4.2 Demographic data

Table 4 summarises the demographic data of the sample analysed. The total number of patients reviewed were 218 (n=218) of which 59.17% (n=129) were adults and the remaining 40.83% (n=89) were paediatric patients. In the context of this study, the term 'adult patients' refers to patients who are above 18 years of age, while 'paediatric patients' refer to patients who are 18 years or younger. Overall, more males (54.59%) were prescribed meropenem when compared to females (45.51%). The average age for adults was 46.51 years and SD = 16.05 years (standard deviation). The average age for paediatrics overall was 9.57 months and the SD = 2.65 years. The results also indicated that the ward with the highest usage of meropenem was in the Intensive Care Units (paediatrics) with a total of 31.19% (n=68) cases reported.

Table 4: Demographic characteristics of patients in study (n = 218)

Variables	Number (n)	Percentage (%)
Age		
Adults (>18 years)	129	59.17
≤ 1 years	79	36.24
2 – 5 years	5	2.29
6 – 10 years	2	0.92
11 – 18 years	3	1.38
Gender		
Male	119	54.59
Female	99	45.41

Hospital Wards		
Intensive Care Units (Adults)	66	30.28
Intensive Care Units (Paediatrics)	68	31.19
General Medical Wards (Adults)	66	30.28
General Medical Wards (Paediatrics)	12	5.50
Obstetrics and gynaecology Wards	6	2.75

4.4 Meropenem usage

4.4.1 Diagnosis

The primary diagnosis is recorded on both the application for non-formulary items (Appendix B) as well as the patient prescription. The diagnosis recorded is often the initial diagnosis made by the clinician and often may not provide the comprehensive reason for prescribing and administering meropenem. The guidelines and approved diagnosis which warrants the administration of meropenem can be found in both the STG (Table 1) and EML (Table 2).

The general data collection tool (Appendix D), which has been adapted from the SAASP, classified the diagnosis into 7 different categories: pneumonia, meningitis, line infection (infection that occurs when bacteria enter the blood stream through an intravenous line), intra-abdominal infections, cellulitis, urinary tract infections (UTI) and other. Table 5 below shows the results recorded for the reviewed patients.

Table 5. Clinical characteristics of patients in study (n=218)

Diagnosis	**Adults (n=129)**		**Paediatrics (n=89)**		**Total**	
	Number (n)	Percentage (%)	Number (n)	Percentage (%)	Number (n)	Percentage (%)
Pneumonia	34	26.36	1	1.12	35	16.05
Meningitis	5	3.88	1	1.12	6	2.75
Line Infection	6	4.65	1	1.12	7	3.21
Intra-Abdominal Infection	18	13.95	2	2.25	20	9.17
Cellulitis	0	0	0	0	0	0
Urinary Tract Infection	1	0.78	2	2.25	3	1.38
Other	65	50.38	82	92.14	147	67.43

The results from the retrospective study indicate that the most common indication for meropenem in both adult and paediatric patients were classified as 'other'. To better understand this result Table 6 indicates a breakdown of the category indicating the specific diagnosis as recorded in the application for non-formulary items.

Table 6. Further diagnosis of meropenem as per patient file studied.

Diagnosis	**Adult (n=65)**		**Paediatrics (n=82)**	
	Number (n)	Percentage (%)	Number (n)	Percentage (%)
Endophthalmitis	1	1.54	0	0
Sepsis	64	98.46	82	100

Evident in Table 6, the most common indication for use of meropenem is sepsis, with the occurrence in adults amounting to 49.61% of total indications and 92.14% of paediatric indications. In adult patients, the second most common indication for meropenem was pneumonia (26.36%) and for paediatric patients it was intra-abdominal infections (2.25%) and line infection (2.25%).

The following observations were also made:

- There was one case of endophthalmitis, which is an infection of tissues or fluid inside of the eye amongst adult patients.
- Of the patients who were diagnosed with pneumonia, 13 (5.96%) patients developed pneumonia secondary to Coronavirus disease (COVID) 19.
- One patient (0.49%) developed sepsis secondary to Tuberculosis (TB)
- One patient (0.49%) developed sepsis secondary to COVID-19
- Four patients (1.83%) developed both pneumonia and sepsis secondary to COVID-19

Meropenem was utilised as a therapeutic intervention for the secondary diagnosis in the aforementioned instances.

4.4.2 Source of infection

The source of infection is defined by the CDC as 'the person, animal, object or substance from which an infectious agent passes or is disseminated to the host (immediate source).' Results indicated that there are 3 types of sources for infection in the sample analysed, namely:

- Hospital acquired;
- Community acquired and
- Unknown origin as depicted in Table 7.

Hospital acquired infections, also referred to as nosocomial infections, are defined as infections that are not present or in the incubation stage at the time of admission to the hospital. Infections that are detected within the initial 48 hours of hospitalization are categorized as community acquired (Monegro *et al.,* 2023). This data is documented by the prescriber in the patient's file as well as the motivational forms.

Results indicate that 24.03% of the cases where meropenem in adults was prescribed and administered, that the source of infection was hospital acquired and only in 3.37% of cases for paediatric patients. Community acquired infections, which were only present in adult patients, was 3.88%. Unfortunately, for both adult (72.09%) and paediatric patients (96.63%), majority of the source of infection was not recorded and thus classified as unknown.

Table 7. Source of infection per patient files studied

Source of infection	**Adult (n=129)**		**Paediatrics (n=89)**	
	Number (n)	Percentage (%)	Number (n)	Percentage (%)
Hospital Acquired	31	24.03	3	3.37
Community Acquired	5	3.88	0	0
Unknown	93	72.09	86	96.63

4.4.3 Indication for treatment

The indication of treatment is based on a medical condition, sign or symptom that leads to recommendation of treatment. Treatment can be one of the following:

- Empirical – treatment given without precise knowledge or nature of the condition. It is usually based off experience.
- Prophylactic – medication administered to prevent disease.
- Definitive – Final treatment that is made after receiving results of test (such as microscopy, rapid microbiological culturing and microorganism susceptibility testing of patient specimens and biopsies).
- MDR – These are bacteria that are resistant to multiple antibiotics and often require more aggressive treatment forms. This is part of definitive treatment.

The data is recorded in the motivation forms. The prescribing physician would specify whether culture and sensitivity tests have been ordered. If the tests indicate susceptibility of the organism to meropenem, this would be noted. Otherwise, the prescriber would indicate that, based on patient signs and symptoms, empirical treatment would commence with meropenem while awaiting culture and sensitivity test results, with the intention of modifying treatment once definitive results are obtained.

As seen in Table 8 below, it was observed that meropenem was the preferred choice for empirical therapy in adult patients (65.12%), whereas most clinicians treating paediatric patients opted for meropenem only once treatment is definitive (55.06%).

Table 8. Indication of treatment

Indication for treatment	**Adult (n=129)**		**Paediatrics (n=89)**	
	Number (n)	Percentage (%)	Number (n)	Percentage (%)
Prophylactic	2	1.55	1	5.62
Empirical	84	65.12	33	37.08
Definitive	40	31.01	49	55.06
Unknown	3	2.33	6	6.74

During the study period 23 cases of MDR pathogens were observed for adults and 19 cases for paediatric patients.

4.4.4 Duration of treatment

The duration of treatment refers to the number of days, weeks, months, or years that a patient should receive medication. This is dependent on the severity of the infection and response rate of the patient (Seffinger and Hruby, 2007).

As per the National STG guidelines outlined in Chapter 2.6; Table 1, adult patients with conditions like meningitis should receive treatment for seven days, while patients with hospital acquired pneumonia and *Haemophilus influenza* should receive treatment for 10 days. The data presented in Table 9 suggests that meropenem is commonly administered to paediatric patients for 8 to 14 days (35.96%), while adult patients are generally given a course of four to seven days (41.86%).

Table 9. Average duration of therapy (days) for adult and paediatric patients,

Duration of treatment (days)	**Adult (n=129)**		**Paediatrics (n=89)**	
	Number (n)	Percentage (%)	Number (n)	Percentage (%)
< 3	3	2.33	0	0
4 to 7	54	41.86	9	10.11
8 to 14	27	20.93	32	35.96
15 to 21	5	3.38	2	2.25
22 to 28	1	0.78	0	0
> 28	1	0.78	0	0
Unknown	38	29.46	46	51.69

4.4.5 Meropenem dosing and frequency

Within the field of pharmaceuticals, the term "dose" refers to the precise amount of medication that should be taken during a single administration. This aspect of medication compliance is particularly crucial, as taking the correct dose can mean the difference between effective treatment and potential harm. Additionally, "frequency" denotes the

recommended intervals between successive administrations of the medication, which is also a vital parameter that warrants close monitoring, as it can greatly impact the medication's efficacy.

The purpose of the two Tables, Table 10 and 11, is to provide an overview of the most favoured dosage and administration frequency of meropenem at the facility. According to Table 10, many prescribers tend to prescribe a dose of 1g (76.74%) and a frequency (94.57%) of every eight hours when administering meropenem to adult patients. Out of the 129 adult patients who received meropenem, only two patients were given a loading dose of 2g followed by a dose of 1g every eight hours.

Table 10. Overview of dosage and frequency of therapy in adult patients (n=129)

	Adults (n=129)	
Dosage (g)	Number (n)	Percentage (%)
0,5	19	14.73
1	99	76.74
2	11	8.53
Frequency		
24 - hourly	0	0
12 - hourly	5	3.88
8 - hourly	122	94.57
6 - hourly	1	0.76

When administering meropenem to paediatric patients, it is imperative to calculate the appropriate dosage based on their weight accurately. While prescribers have omitted the weight of paediatric patients on the motivational form, this crucial information is accessible via the patient file to both prescribers and pharmacists responsible for initially dispensing meropenem, and the pharmacist will only do so once all necessary information has been provided and verified.

Based on the dosing patterns of prescribers outlined in table 11, it appears that 40.45% of paediatric patients were given a dosage between 51mg and 150mg of meropenem.

Additionally, it was noted that an overwhelming majority of these patients (98.88%) received their medication at eight-hour intervals.

Table 11. Overview dosage and frequency of therapy in paediatric patients (n=89)

	Paediatric (n=89)	
Dosage (mg)	Number (n)	Percentage (%)
<50	34	38.2
51-150	36	40.45
151-300	9	10.11
>300	10	11.24
Frequency		
24 - hourly	0	0
12 - hourly	0	0
8 - hourly	88	98.88
6 - hourly	1	1.12

4.4.6 Microbiological cultures

A microbiological culture is the process of culturing bacteria in a regulated environment in order to identify the species. Microbiological cultures play an essential role in the diagnosis and treatment of many diseases. Ideally, microbiological cultures should always be requested when infection is suspected prior to the commencement of antibiotics (Katz *et al.,* 2021).

During the study period, the result indicates overall for both adult and paediatric patients blood culture and sensitivity tests were requested prior to the administration of antibiotics (adults 50.39%; paediatrics 71.91%). A small percentage of clinicians (treating adult patients 10.10% and treating paediatric patients 1.12%) did not request sensitivity tests.

Table 12. Timing of request for microbiological cultures in relation to antibiotic administration

Request for microbiological cultures	**Adult (n=129)**		**Paediatrics (n=89)**	
	Number (n)	Percentage (%)	Number (n)	Percentage (%)
Before administration of antibiotics	65	50.39	64	71.91
After administration of antibiotics	51	39.53	24	24,72
Not requested	13	10,1	1	1,12

4.4.6.1 Microorganisms culturing

In this study, a total of 30 different types of microorganisms were cultured, with 21 types found in adults and 21 types in paediatric patients. Of the microorganisms cultured, 34% were gram-negative bacteria and the remaining 66% were gram-positive bacteria. Figures 4 and 5 display the various types of microorganisms cultured in the adult and paediatric populations, respectively.

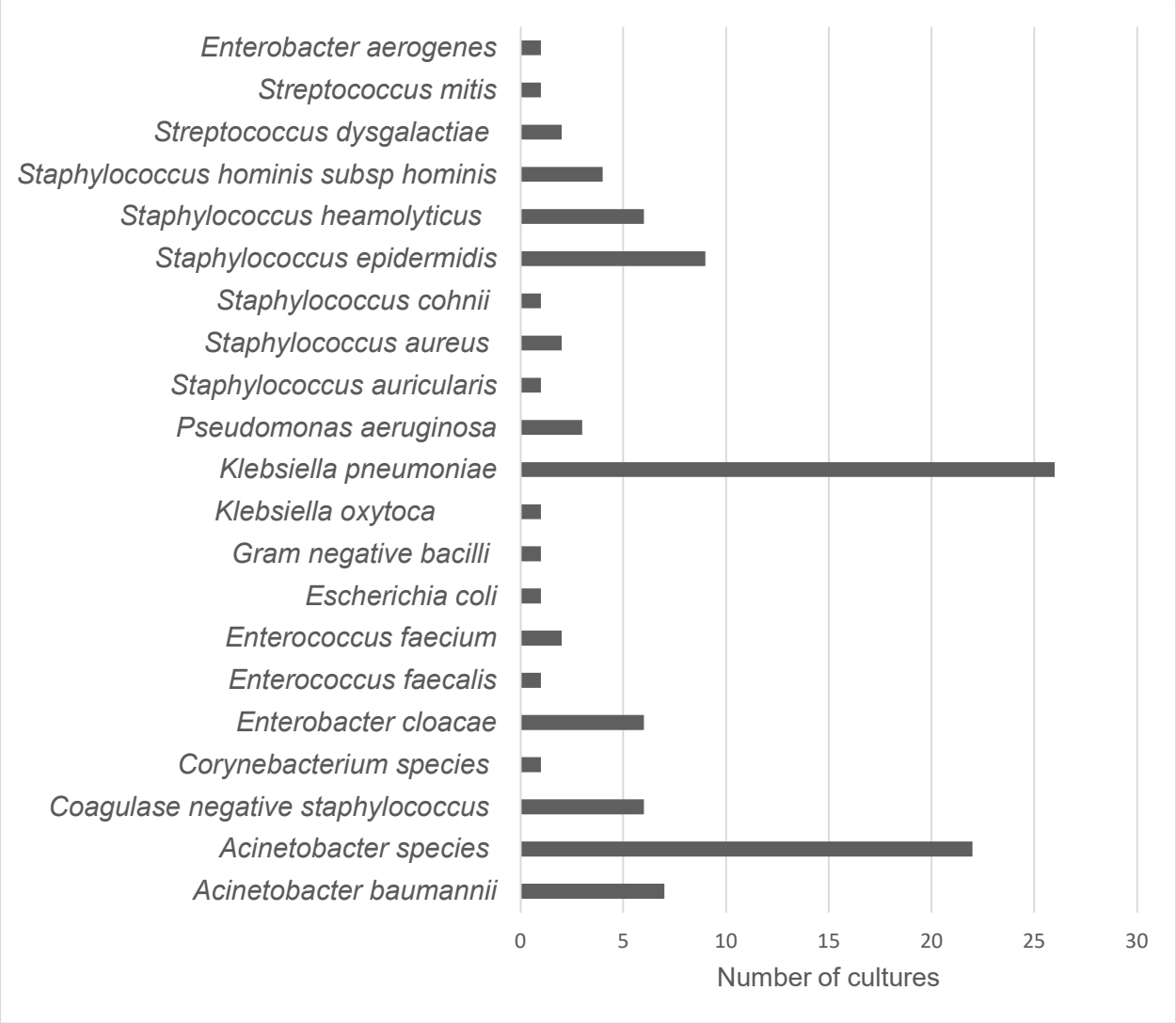

Figure 4. Number of microorganisms for paediatric patients (n=89) during the study period.

Based on the data in Table 12, it is evident that 88 requests received by the NHLS for microbiological cultures, from which 103 microorganisms were identified. The most cultured microorganism was *Klebsiella pneumoniae*, accounting for 25.24% of cases, as depicted in Figure 6.

In the examination of sensitivity outcomes within the paediatric population, it was observed that 42.42% of the bacterial cultures exhibited sensitivity to meropenem, whereas 23.23% demonstrated resistance. The remaining 34.34% of cases were categorised as 'NULL', signifying that sensitivity to meropenem was not assessed.

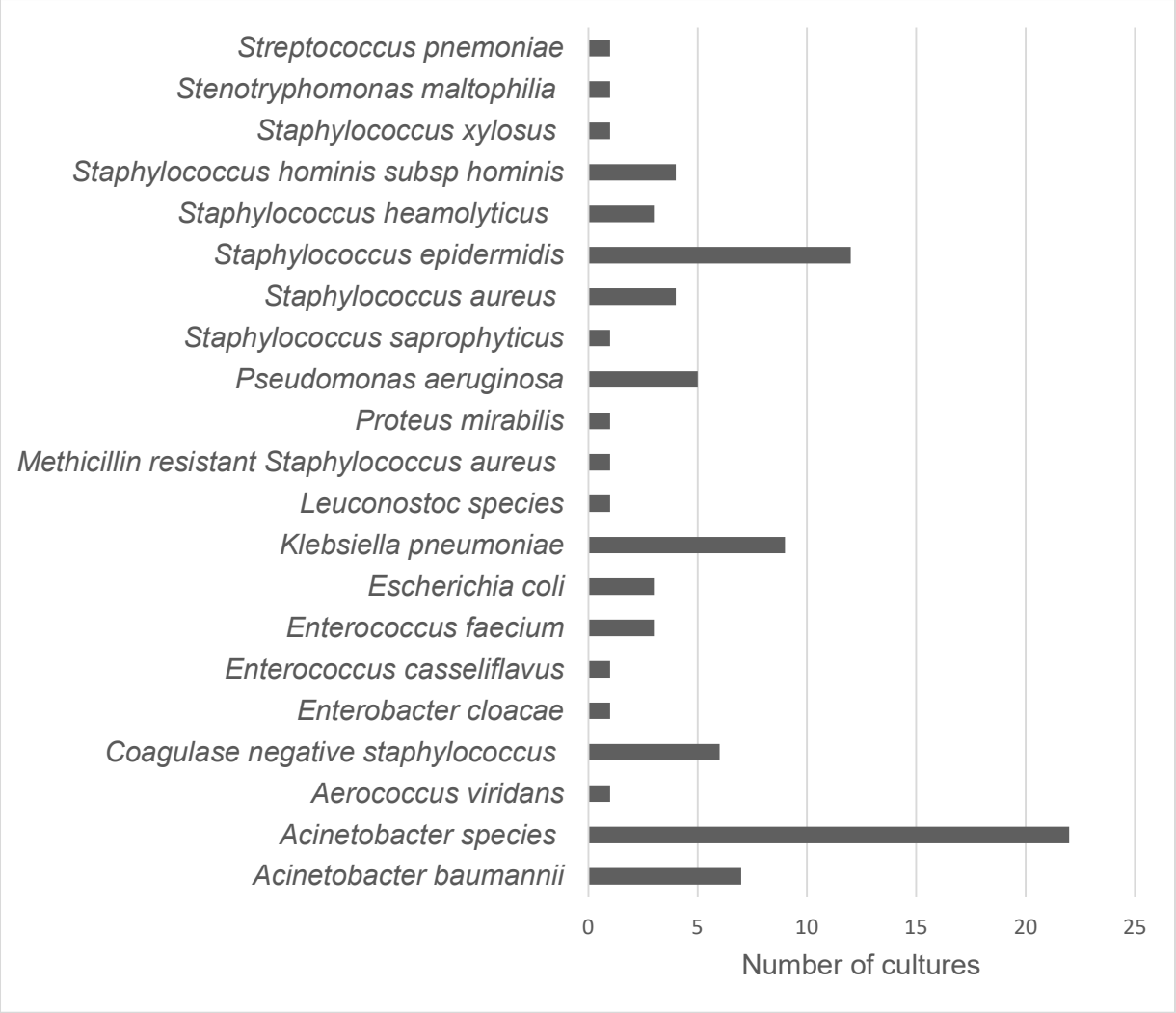

Figure 5. Number of microorganisms for adult patients (n=129) during the study period.

The data in Figure 5 indicates that out of the 88 microorganisms identified, the most common one was the Acinetobacter species at 25%. The sensitivity results from the adult population showed that only 29.03% of the microorganisms were sensitive to meropenem, while 23.66% were resistant. The rest were classified as 'NULL'. Both the paediatric and adult patients had MDR pathogens identified, with the Acinetobacter species, specifically *Acinetobacter baumannii*, being the most prevalent.

4.7 Adherence to public sector guidelines on meropenem utilisation

The adequacy of treatment was evaluated utilising the STG (Table 1) and EML (Table 2) protocols. A concise overview of the outcomes can be observed in Figures 6 presented

below. Table 13 outlines the criteria outlined in both the STG (for adult patients) and EML (for paediatric patients) that were utilised to gauge appropriateness.

Table 13. Summary of criteria utilised to gauge appropriateness of treatment

Overall appropriateness	**Conditions (as per STG) for adult patients**	**Conditions (as per EML) for paediatric patients**
Diagnosis	Febrile Neutropenia, Hospital Acquired Pneumonia, Meningococcal meningitis, Pneumococcal meningitis, Haemophilus influenza	In severe infection, meningitis
Duration	7 to 10 days	Not provided

The prescribing and administration of meropenem was considered appropriate for 53.49% of cases in adult patients (Figure 6). The recommended duration of treatment for meropenem in adults is 7 to 10 days, of which 27.13% of cases fell within this range. Only 14.29% of adult patients were prescribed the dose and frequency according to STG guidelines (2G three times daily intravenously). Overall, when considering the diagnosis, duration, dose and frequency (as stipulated by the guidelines) only 4 patients (3.10%) matched the criteria.

As observed in Table 13, the Essential Medicines List (EML) for pediatric patients does not stipulate a recommended duration of treatment for meropenem. Consequently, prescribers must rely on their clinical expertise and the progression of symptoms to make decisions on a case-by-case basis. An additional aspect often not recorded on motivation forms by prescribers is the patient's weight, although this information is accessible to both the prescriber and the pharmacist responsible for evaluating the prescription.

The absence of this recorded information for paediatric patients presents a challenge in confirming the accuracy of the administered meropenem dosage. Nonetheless, based on the available data, the study is able to infer that meropenem was appropriately prescribed to paediatric patients in accordance with EML guidelines for the correct diagnosis and

frequency. In fact, nearly all paediatric patients (95.51%) received the prescribed frequency of meropenem.

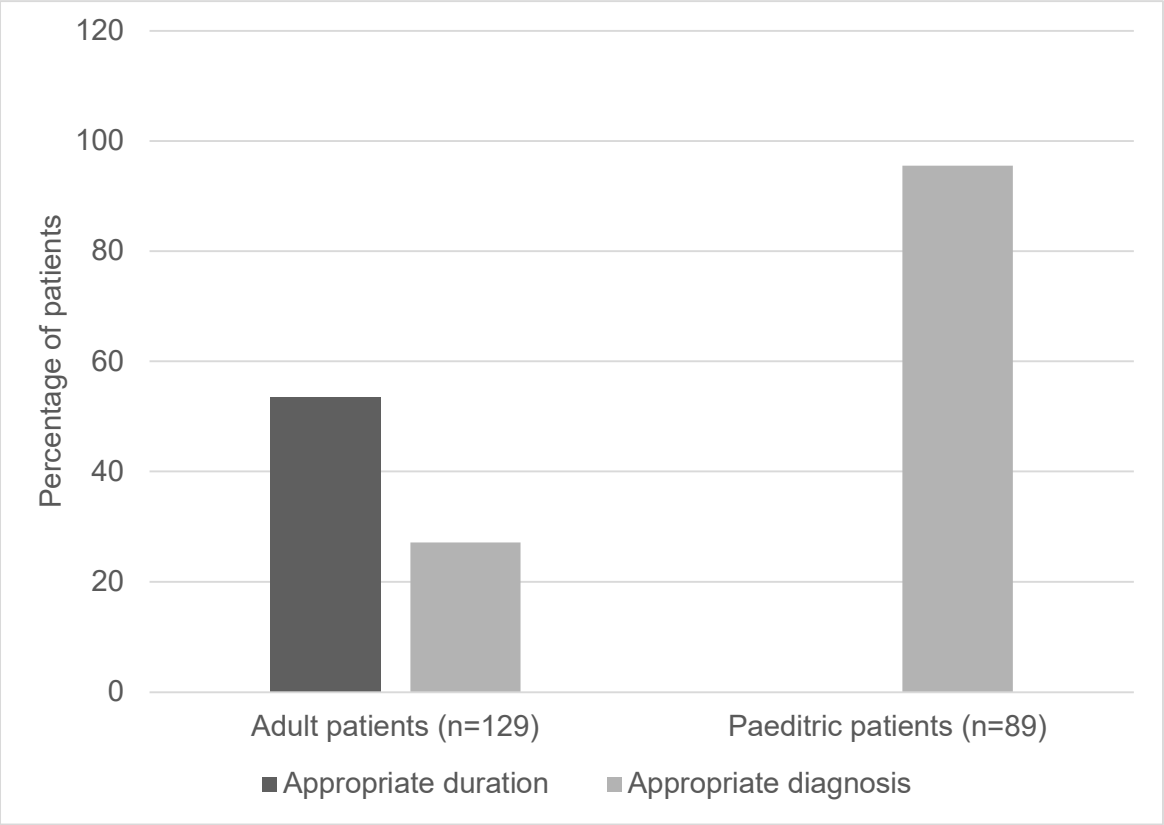

Figure 6. Summary of correctly treated adult patients (n=129) and paediatric patients (n=89) as per STG guidelines.

4.9 Summary

The study revealed that meropenem is commonly used to treat severe infections in both adult and paediatric patients. It was found that the majority of adult patients receive meropenem as an empirical treatment (65.12%), while most paediatric patients receive it as a definitive treatment (55.06%). Interestingly, the source of infection is not consistently documented on patient charts, and paediatric patient weights are often not recorded, making it difficult to assess the appropriateness of the meropenem dosage. Although all prescriptions analysed were valid, only a small percentage of treatments were deemed appropriate. Additionally, clinicians frequently request microbiological cultures and blood

sensitivity tests before prescribing antibiotics. The study also found that *Klebsiella pneumoniae* was the most common bacteria cultured in paediatric patients, while *Acinetobacter* species was prevalent among adults.

CHAPTER 5: DISCUSSION

5.1 Introduction

Antimicrobial agents are one of the most utilised drug classes in the hospital setting particularly in wards such as the Intensive Care Units (ICU) including Adult ICU (AICU) and Neonatal ICU (NCU). According to Khan *et al*. 2014, it is often observed that the irrational utilisation of antibiotics has led to an upsurge in the mortality and morbidity rate in the community which ultimately leads to the development of antibiotic resistance.

The healthcare domain is plagued by the prevalent misuse and overuse of antibiotics, leading to adverse consequences such as antibiotic resistance. The appropriate use of antibiotics can be promoted using antimicrobial stewardship programs such as drug utilisation evaluation studies (Khan *et al*. 2014).

Whilst there have been numerous drug studies performed in South Africa no previous studies investigated the use of meropenem at this institution. The goal of this study was to evaluate the appropriateness of meropenem in a tertiary institution in the public sector.

5.2 Demographic data

The majority of patients who received meropenem were adults, which aligns with the findings of a recent study conducted by Steffens *et al.* in 2020. This observation raises concerns about the limited research on the use of meropenem in paediatric patients, potentially leading to insufficient resources for this demographic. Unlike adults, there are numerous studies and recommendations on meropenem dosage, children have very few resources available in this regard, as highlighted in a study conducted by Wang *et al.* in 2011. An explanation is explored by Asultan *et al.* in 2023, which explains that various clinical factors affect meropenem pharmacokinetics (PK) in paediatric patients, such as increased capillary leakage and aggressive fluid resuscitation during sepsis, which substantially increases the volume of distribution.

This study found that the average age of paediatric patients administered meropenem was 9.57 months. Asultan *et al.* also mention that limited data are available on meropenem

developmental PK in neonates and young infants compared to older children (Asultan *et al.,* 2023).

Despite the restricted approval for the use of meropenem in paediatric patients, a considerable number have received the drug. In a study conducted by Buck (1998), the effectiveness of meropenem was compared to cefotaxime, revealing that 98% of meropenem-treated patients exhibited a satisfactory clinical response, as opposed to 93% of cefotaxime-treated patients. Additionally, meropenem is favoured for paediatric patients due to its lower affinity for GABA receptors, reducing the potential for central nervous system (CNS) effects (Buck., 1998).

Furthermore, the study also revealed that male patients received meropenem more frequently than their female counterparts, pointing to potential gender disparities in treatment. The complexity of gender differences in antibiotic use is noteworthy, as they are often influenced by socioeconomic factors rather than biological disparities, as emphasised by Pham-Duc and Sriparamananthan (2021).

5.3 Utilisation pattern of meropenem

Throughout the year 2021, meropenem was prescribed and administered in a total of 218 cases within the institution. The utilisation pattern of meropenem differed among various departments, with the greatest frequency of usage noted in intensive care units. Following closely behind were general medical wards, while obstetrics and gynaecology wards accounted for a smaller percentage of usage.

According to Sanhoury and Eldalo (2016), the high consumption of meropenem in intensive care wards is due to the unique population with a diverse disease process. These patients are critically ill and at a higher risk of developing nosocomial infections, making an antibiotic such as meropenem (being broad-spectrum, well tolerated, and highly susceptible) the ideal choice for these patients.

The neonatal intensive care unit showed the highest usage of meropenem in paediatric patients, which mirrors the trend seen amongst the adult population, indicating its effectiveness as noted by Sanhoury and Eldalo (2016) and Buck (1998). Despite Wang *et*

al.'s (2021) finding of insufficient literature and guidelines for meropenem use in paediatric patients, clinicians continue to rely on their clinical experience when treating young patients. This observation is also reflected in the current guidelines in South Africa, such as STG and EDL.

5.4 Diagnosis

Throughout the therapeutic process, the initial diagnosis documented on the non-formulary items form and in the patient's file remained unchanged. This is a common practice among clinicians who often overlook updating the diagnosis during the treatment period, thus missing out on potential new findings. As mentioned by Pollack *et al*., 2013, an integral part of antibiotic stewardship is the recording of the reason of antibiotic initiation. However, it is just as important to note the decision to continue antibiotics. It is essential to reassess the need for antibiotics as too often antibiotics are continued without critical reappraisal (Pollack *et al*., 2013). Documenting these changes will help monitor and implement better policies.

The findings of this study indicate that meropenem is commonly used to treat sepsis in both adults and paediatric patients. Studies by Zhao *et al.* in 2017 and Raza *et al.* in 2022 have shown that meropenem is effective in treating sepsis and septic shock. Research also indicates that continuous infusion of meropenem during sepsis treatment is clinically effective and leads to a shorter duration of therapy with better bacteriological outcomes (Zhao *et al.,* 2017). Furthermore, meropenem has been recommended for use in neonates with sepsis (Lutsar *et al.,* 2020).

In 2019, Russel *et al.,* conducted a study on the tractable targets for meropenem sparing AMS interventions. The findings of this study indicated that meropenem was used in the treatment of respiratory infections (such as pneumonia), UTI, line infections, intra-abdominal infections and sepsis with the majority of cases being used in respiratory infections. This is in line with the findings this current study that adult patients were administered meropenem for pneumonia. Pneumonia, as defined by the National Heart, Lung and Blood Institute of America, “is an infection that causes the air sacs or alveoli of the lungs to fill up with pus and the cause maybe bacterial, viral or fungal”. Pneumonia can be categorized as either community acquired pneumonia (CAP) or hospital acquired pneumonia (HAP). It is crucial to

differentiate between the two due to the involvement of distinct causative agents, necessitating the use of different antimicrobial therapies (Van Vught et al., 2016).

An effective pneumonia treatment regimen involves the use of antibiotics that target anaerobic bacteria. According to a study by Tokuyasu *et al.* (2009), meropenem is recommended for this purpose. Their research, which examined 63 adult patients with pneumonia, revealed that meropenem was successful in treating 61.63% of the cases. These findings provide support for the use of meropenem as a treatment for pneumonia, in line with STG guidelines.

The research findings suggest that meropenem was administered to treat pneumonia as a secondary condition to COVID-19. This may be attributed to the scarcity of evidence indicating bacterial superinfection in many cases, despite COVID-19 being viral in nature. Consequently, healthcare providers faced challenges in distinguishing between the two conditions, leading to the widespread use of antibiotics (Molla *et al.,* 2021 and Al-Hadidi *et al.,* 2021).

In Molla *et al.'s* (2021) investigation into antibiotic prescription patterns during COVID-19 in Bangladesh, it was observed that meropenem (40.90%) was the second most commonly prescribed antibiotic after ceftriaxone (53.88%).

Another condition approved for the use of meropenem is meningitis (meningococcal and pneumococcal meningitis). Meningitis, as defined by the CDC, is the inflammation of the protective membranes covering the brain and spinal cord. Meropenem is used specifically in the treatment of bacterial meningitis. A study conducted in 2019 by Ohata *et al*. assessed the effectiveness of meropenem in treating bacterial meningitis in paediatric patients. The research involved an analysis of clinical data of 154 patients, which revealed that at least 23.37% of patients achieved a satisfactory clinical cure whilst on meropenem.

In Neonatal Intensive Care Units (NICUs), it is often necessary to implant Central Vascular Catheters (CVCs) in newborns to monitor and administer fluids, medications, parenteral feeding, and other treatments. While CVCs offer numerous benefits, the multiple entry points created through the skin barrier, along the catheter's exterior surface, and through its lumen

can increase the likelihood of infection problems, known as line infections (Piersigilli *et al*., 2022). According to the study, a relatively low number of adult and paediatric patients were treated with meropenem to combat line infections.

5.5 Source of infection

As previously mentioned, the source of infection may have 3 origins namely: hospital acquired, community acquired and unknown. From the data collected, a large number of cases where meropenem was prescribed and administered were of unknown origin.
In many cases, the attending clinician neglected to mention the source of the infection in the patient file as well motivational forms. As a result, the true source of such infections was lost.

The second common source of infections for patients who were prescribed and administered meropenem was hospital acquired. Nosocomial infections, also known as hospital-acquired infections, are infections that are acquired during a hospital stay. These infections are often not present at the time of admission but may be incubating. Typically, symptoms of these infections become evident 48 hours after admission.

Patients who are critically ill, especially patients admitted into intensive care wards are immunocompromised and hence more susceptible to hospital acquired infections. Although some patients in medical wards have also been diagnosed with hospital acquired infections, it can be seen that the distribution of pathogens vary according to the clinical setting, patient characteristics and health setting (McFee, 2009).

5.6 Indication of treatment

Meropenem being a broad-spectrum antibiotic, is often used for empirical treatment in critically ill patients (Sanhoury and Eldalo, 2016). The findings of this study are consistent with this study as majority of adult patients were prescribed meropenem empirically. The reason why meropenem is often prescribed empirically is because roughly one third of adult patients are admitted to the ICU. In these cases, patients are critically ill with a high likelihood of infection, hence physicians lean towards prescribing meropenem.

The results of this study support the finding of a similar study performed by Khan *at al.*(2014). Khan *et al. (2014) also* looked at the use of meropenem in a tertiary institution in

Iran, the results reflected that 49.43% of cases were treated empirically in comparison to the 11.44% which were definitive diagnosis.

However, this is contrary to the findings of the paediatric patients. The study results showed that in most cases involving paediatric patients, meropenem was administered by clinicians only when a definitive diagnosis had been made. A reason for is as mentioned by Wang *et al*.(2021), there are fewer guidelines with regards to meropenem dosing in paediatric patients. Although in the study meropenem was commonly despite the lack of safety and efficacy data, it is considered an off-label use especially in infants < 3 months (Cohen-Wolkowiez *et al.,* 2012). There are also central nervous system safety concerns in the use of meropenem in infants. As such clinicians ensure the definitive cause of disease in children before prescribing and administering meropenem.

5.7 Duration, dose, and frequency of treatment

There have been numerous efforts to improve antibiotic use in hospitals, however these efforts are constantly being hampered by the complexity of medical decisions surrounding antibiotic administration (Pollack *et al.,* 2013). When determining the duration, dose and frequency of meropenem clinicians take into account the severity of infection, prevalence of resistance to other antimicrobial agents and the risk/benefit ratio of treatment.

The results from this study indicated that a small percentage of adult patients received a dose of meropenem that was considered within guidelines when compared to the STG guidelines (Table 1). However, it is imperative to consider the impact of renal clearance on the appropriate dosage of meropenem. In this study adult patients who received meropenem were admitted in ICU and as previously mentioned ICU patients often have multiple co-morbidities. In a study conducted by Sanhoury and Eldalo (2016), 29.60% patients admitted into ICU suffered from moderate to severe renal failure. In another study conducted by Tsai *et al.,* 2016, it was demonstrated that renal function is the most important factor of meropenem pharmacokinetics and the dosing regimen should be adjusted according to the patient renal function. This study revealed that a significant proportion of adult patients were administered a lower dosage of meropenem. The renal function data was unavailable from the NHLS CDW database, rendering it inappropriate to draw conclusions regarding the appropriateness of the meropenem dosage for this study. It is worth noting that the

prescriber had access to this information at the time of diagnosis, enabling the appropriate prescription of meropenem for the patient. Additionally, this information is also available to the pharmacist who conducts the initial evaluation and dispenses the meropenem.

The guidelines for dosing medication in paediatric patients are limited, but the dose of meropenem is determined by the patient's weight. Clinicians treating paediatric patients often rely on their clinical experience to make decisions (Sanhoury and Eldalo, 2016). Children have specific PK-PD parameters, including a larger volume of distribution for hydrophilic medications and rapid renal clearance (Imburgia and Kussin, 2022). Imburgia and Kussin (2022) analysed studies on dosing meropenem in paediatric patients and found that a dose of 40mg/kg every 8 hours for 7 days was associated with higher rates of clinical improvement in cases of late-onset sepsis and meningitis compared to a dose of 20mg/kg for 7 days.

The EML guidelines (Table 2) which is used as the guidelines on the usage of meropenem for paediatric patients, no duration of treatment is recommended, instead clinicians are encouraged to take into account factors such as: type of infection to be treated, severity of infection and clinical response when determining the duration of treatment.

5.8 Microbiological cultures

According to a 2019 study conducted by Russell et al., it is crucial to conduct microbiological and sensitivity tests prior to initiating antibiotic treatment. The results of this study support the notion that as findings indicate that in the majority of cases, both adult and paediatric patients had undergone microbiological cultures prior to receiving antibiotics.

It was observed in the Russell *et al*.(2019) study that microbiological blood cultures were feasible in only 29% of the cases and were not carried out in the remaining cases. Similarly, in this study found that a small percentage of adult and paediatric patients did not have any request for microbiological cultures and sensitivity tests.

The study identified cases where it was unclear whether the prescriber had specifically requested culture and sensitivity tests, particularly among the pediatric population. This discrepancy can be attributed to the fact that the NHLS CDW only provided access to blood

culture results for the year 2021. It is plausible that the tests were requested in the latter part of 2021, and the results were only accessible in 2022. This limitation pertains to data collection, as prescribers would have access to these results regardless of a specific time frame.

5.8.1 Microorganisms cultured

The results from this study indicated that the most common type of bacteria cultured was the Acinetobacter species, all of which were identified as *Acinetobacter baumannii*. *Acinetobacter baumannii* is an opportunistic pathogen that is commonly found in the health care setting. It has the ability to colonise wide surfaces and is able to survive for prolonged periods under a variety of environmental conditions (Ibrahim., 2019). *Acinetobacter baumannii* is known for its capacity to cause a spectrum of infections, encompassing lower respiratory tract, blood, urinary tract, and wound infections. Moreover, it possesses the capability to develop resistance to a broad array of antimicrobial agents, including meropenem (Ibrahim, 2019). The review conducted by Ibrahim, 2019; stated that in order to combat this pathogen, the administration of other antibiotics such as colistin may be necessary. This is in line with the findings of this study. A total of 5 patients who were identified to be infected with MDR *Acinetobacter baumannii* were administered colistin in addition to meropenem.

In paediatric patients, *Klebsiella pneumoniae* is the most commonly found bacteria. It has been linked to diseases such as bacteremia and neonatal sepsis (Little *et al.,* 2014). Studies suggest that the bacterial infections often predispose vulnerable patients with significant exposure to hospital environment. Recent findings show increasing prevalence in pediatric wards with strains different from those found in adult patients (Little *et al.,* 2014; Zhou *et al.,* 2022).

5.9 Adherence to guidelines

As seen from the results in this study a small percentage of patients were administered the meropenem (in terms of diagnosis, dose, duration and frequency) in line with the recommedations as per the guidelines stated in the STG. It has been found that the prescribing practices of antibiotics in South Africa are far from acceptable thus the need to use more specialised antibiotics such as meropenem. In a study conducted by Paruk *et al.,*(2012); it was noted that 72% of patients admitted in ICU were prescribed inappropriate

duration of antibiotics thus demonstrating the lack of insight and knowledge regarding antibiotic use.

The 2016 study by Sanhoury and Eldalo uncovered persistent shortcomings in certain medical domains, highlighting problematic areas that do not meet established standards and guidelines. One key issue identified in this study was the difficulty in accurately assessing the appropriateness of treatment for both adult and paediatric patients. Comparing the STG and EML guidelines, only a small number of adult and paediatric patients met the criteria. However, limitations such as the unavailability of renal blood test results (creatinine clearance) for adult patients and the lack of recorded weight for paediatric patients make it challenging to make accurate assessments of treatment appropriateness.

As a result many times, clinicians use antibiotics without determination of the exact infection assuming patients who are critical condition warrant the use of broad spectrum antibiotics. Treatment is not based on guidelines and standards but rather on clinical experience (Sanhoury and Eldalo., 2016).

5.10 Summary

Based on the findings of this study, meropenem is often the antibiotic of choice in critically ill patients. In adult patients it is prescribed more empirically compared to paediatric patients where meropenem therapy is more definitive. It can also be noted that clinicians do not base therapy on guidelines but as literature suggests, treatments are likely decided based on clinical experience. The microorganisms being cultured indicate the need for adequate antibiotic stewardship measures to be put in place.

CHAPTER 6: CONCLUSION

6.1 Introduction

This section outlines the main findings of the study, followed by an exploration of its limitations and recommendations.

6.2 Conclusion

This study aimed to assess the utilisation pattern of meropenem in treating patients at a tertiary hospital located in the North West Province of South Africa. This was achieved through the retrospective review of patient records.

Meropenem, a potent antibiotic, is extensively prescribed in this institution, specifically in the ICU wards, for treating severe infections such as pneumonia, meningitis, and sepsis. The findings of the study revealed that the most cultured microorganisms were *Klebsiella pneumoniae* and *Acinetobacter baumannii*. Additionally, five patients were diagnosed with multi-drug resistant (MDR) *Acinetobacter baumannii* infection. However, the study also highlighted several areas of concern that require attention.

Despite meropenem being a potent antibiotic intended only for specific diagnoses, it was the most frequently prescribed empirical treatment. In most instances, prescribers failed to fully identify the source of the infection. These findings suggest that prescribers are not adhering to the recommended guidelines for the use of meropenem as outlined by the STG and EDL. While microbiological and sensitivity tests were requested in the majority of cases for both adult and paediatric patients, there were instances where they were not requested at all. In most cases, the average duration of treatment for adult patients was deemed appropriate when compared to the STG guidelines. However, no duration guidelines were provided for pediatric patients, leaving prescribers to exercise their discretion. Particularly concerning (especially in paediatric patients) were the cases where the duration of treatment was unknown. The significant prevalence of unidentified sources of infection and uncertain treatment duration may indicate an absence of treatment modifications, even subsequent to the receipt of blood cultures.

The study's findings suggest that meropenem is often administered without following evidence-based assessment criteria. These results highlight the crucial need for adhering to established protocols and guidelines for the use of meropenem to maximize its effectiveness and minimize the development of antibiotic resistance.

To achieve rational use of meropenem and reduce antibiotic resistance, it is imperative to implement continuous medical education, functional therapeutic committees, and regular drug utilisation evaluation programs. Clinical pharmacists can play a crucial role in facilitating these initiatives, particularly in areas such as drug selection, dose optimization, and monitoring adverse effects. By collaborating with other healthcare providers, clinical pharmacists can help ensure the appropriate use of antibiotics and promote better patient outcomes.

6.3 Study limitations

The following study limitation should be noted.

- Missing data
    - Incomplete application for non-formulary items made data collection more difficult.
    - The diagnosis and reason for meropenem initiation was not regularly documented.
    - The absence of recorded weight data for pediatric patients has posed a challenge in determining the appropriateness of therapy. It's important to note that this limitation is specific to the study. Prescribers have access to this information when prescribing meropenem, and pharmacists have access to it when dispensing the medication.
    - Prescribers did not report any co-administration of antibiotics on the motivational forms.
- Time and resource constraint
    - The period of the study was short and thus this study only provides a brief view into meropenem usage
- COVID-19
    - Many patients who were diagnosed with COVID-19 presented with multiple ailments.

    - Lack of guidelines to treat critically ill patients diagnosed with COVID-19.
- Limitations on lab results
    - Access to blood culture results for the year 2021 was only available through NHLS CDW. However, blood cultures that were requested in late 2021 and had results given in 2022 were not accessible.
    - The NHLS CDW only authorized the utilization of microscopy, culture, and sensitivity tests specifically for meropenem. Consequently, other blood test results were not obtained and thus could not be incorporated into this study.

6.4 Recommendation from this study

Upon reviewing the data from this study, the following recommendations have been identified that could potentially enhance the utilisation of meropenem.

- Properly documenting the initial diagnosis and tracking the progress of patients in their respective files is of utmost importance. Furthermore, it is essential to complete motivational forms for each patient and include all necessary information such as weight. This will allow pharmacists to thoroughly review the patient's medical history, thereby improving the management of antibiotics.

- When motivational forms, it's essential to provide thorough and compelling reasons for the request. Specifically, it's recommended to include information about the patient's past antibiotic treatment, blood culture findings, and rationale for the change in therapy. By doing so, pharmacists can make informed decisions regarding the most suitable antibiotics to prescribe.

- In case of patients infected with multi-drug-resistant (MDR) pathogens, it is important to prioritize their blood culture and sensitivity tests. This will enable quick identification of the most suitable antibiotic regimen for the patient, which is crucial in managing infections caused by MDR pathogens.

- Additionally, it is recommended that any antibiotic prescriptions, particularly meropenem, be thoroughly evaluated by a clinical pharmacist upon receipt at the pharmacy. This crucial step guarantees that the prescription is suitable for the patient's ailment and that the proper dosage is being administered. It is also

imperative that the medication is promptly dispensed to guarantee that the patient receives the essential treatment without any unnecessary delay.

- Finally, it is recommended that clinical pharmacists attend ward rounds, particularly those held in the intensive care units. This will facilitate the prescription of suitable antibiotics, as well as the determination of appropriate dosages and frequencies based on each patient's unique condition. With clinical pharmacists present during ward rounds, adjustments to antibiotic regimens can also be made promptly, if required.

- It is imperative for hospitals to establish an antimicrobial stewardship committee that can design and enforce highly specialized standard operating procedures and policies based on the unique needs and characteristics of the hospital's population. Such a committee plays a crucial role in promoting the judicious use of antimicrobial agents, preventing the emergence of drug-resistant pathogens, and ensuring optimal patient outcomes.

6.5 Recommendation for future studies

This findings from this study indicate many practices which are not ideal in curbing the rise of antibiotic resistance or advantageous in the implementation of antibiotic stewardship programs. Further drug utilisation evaluation studies should be conducted in other facilities throughout South Africa to ensure the compilation of a comprehensive set of guidelines.

6.6 Dissemination of findings

The findings presented in this study has been disseminated in a research report as part of the completion of the MSc degree. The information has also been shared with hospital management at a Pharmaceutical Therapeutics Committee meeting with the aim to provide insight on the prescribing patterns of meropenem at this facility. The study will also be drafted as a Journal publication to be published in a reputable journal.

6.7 Summary

The cornerstone of antibiotic stewardship lies in the thorough documentation of information pertaining to the utilisation of antibiotics. This study provided the information regarding the

utilisation of meropenem in this facility for the period of January 2021 to December 2021. The results indicated that there is a difference between guideline recommendations and clinical practice and there is an urgent need to implement effective antimicrobial practices to curb the rising of antibiotic resistance.

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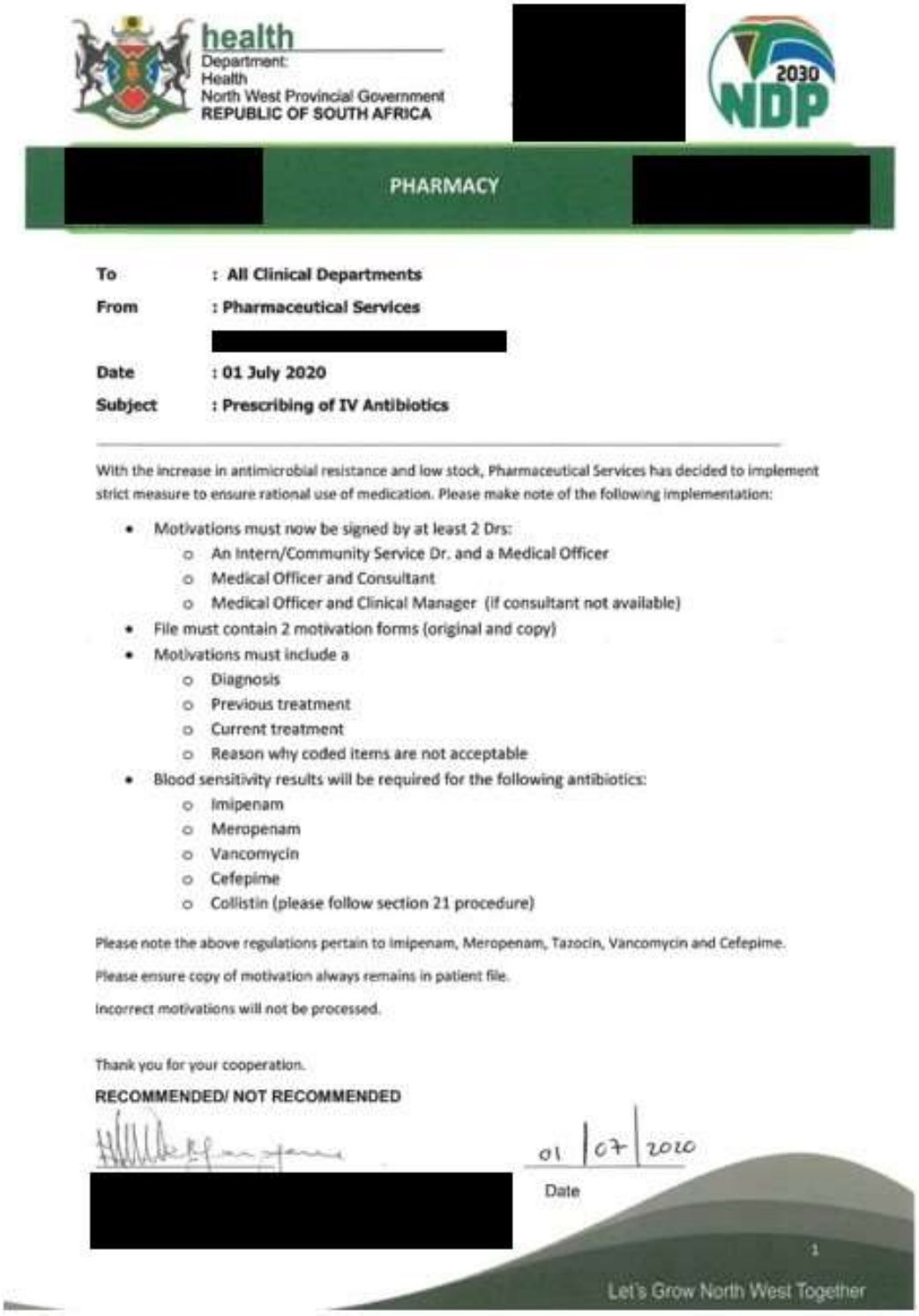
List of appendices

Appendix A: Policy for prescribing of intravenous antibiotics



health
Department:
Health
North West Provincial Government
REPUBLIC OF SOUTH AFRICA

[redacted]

2030 NDP

[redacted] PHARMACY [redacted]

To : **All Clinical Departments**

From : **Pharmaceutical Services**

[redacted]

Date : **01 July 2020**

Subject : **Prescribing of IV Antibiotics**

With the increase in antimicrobial resistance and low stock, Pharmaceutical Services has decided to implement strict measure to ensure rational use of medication. Please make note of the following implementation:

- Motivations must now be signed by at least 2 Drs:
  - An Intern/Community Service Dr. and a Medical Officer
  - Medical Officer and Consultant
  - Medical Officer and Clinical Manager (if consultant not available)
- File must contain 2 motivation forms (original and copy)
- Motivations must include a
  - Diagnosis
  - Previous treatment
  - Current treatment
  - Reason why coded items are not acceptable
- Blood sensitivity results will be required for the following antibiotics:
  - Imipenam
  - Meropenam
  - Vancomycin
  - Cefepime
  - Collistin (please follow section 21 procedure)

Please note the above regulations pertain to Imipenam, Meropenam, Tazocin, Vancomycin and Cefepime.

Please ensure copy of motivation always remains in patient file.

Incorrect motivations will not be processed.

Thank you for your cooperation.

RECOMMENDED/ NOT RECOMMENDED

01 | 07 | 2020

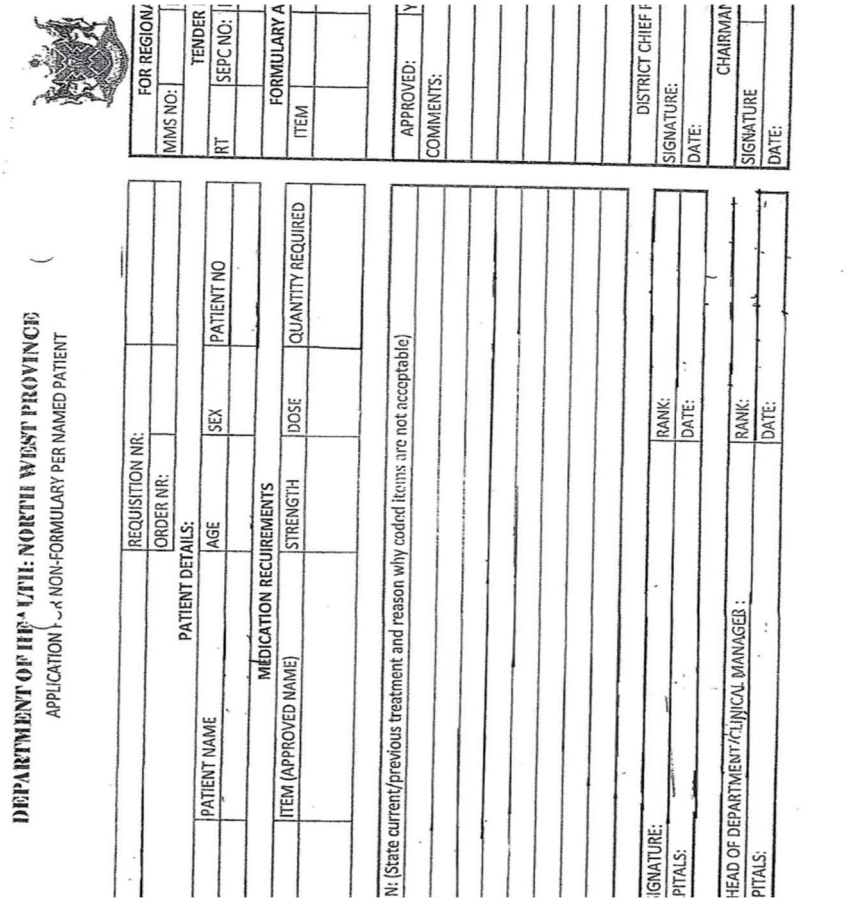
[redacted]

Date

1

Let's Grow North West Together

Appendix B: Application for non-formulary per patient (Motivational form)



DEPARTMENT OF HEALTH: NORTH WEST PROVINCE

APPLICATION FOR A NON-FORMULARY PER NAMED PATIENT

REQUISITION NR:

ORDER NR:

PATIENT DETAILS:

PATIENT NAME	AGE	SEX	PATIENT NO

MEDICATION REQUIREMENTS

ITEM (APPROVED NAME)	STRENGTH	DOSE	QUANTITY REQUIRED

N: (State current/previous treatment and reason why coded items are not acceptable)

IGNATURE: RANK:

PITALS: DATE:

HEAD OF DEPARTMENT/CLINICAL MANAGER : RANK:

PITALS: DATE:

FOR REGIONA

MMS NO: TENDER

RT SEPC NO:

FORMULARY A

ITEM

APPROVED:

COMMENTS:

DISTRICT CHIEF F

SIGNATURE:

DATE:

CHAIRMAN

SIGNATURE

DATE:

Appendix C: Data collection tool to measure appropriateness of prescription

Study number:		
Validity of prescription	**YES**	**NO**
Valid as per requirements stated in Good Pharmacy Practice		
Date		
Patient name and details		
Prescriber name and details		
Prescription validated by pharmacist		
Appropriateness of diagnosis		
Diagnosis appropriate		
Diagnosis		
Dose		
Diagnosis and dosage at per STG		
Adult	**Dosage as per STG**	
Febrile Neutropenia	1 g 8 hourly IVI	
Hospital Acquired Pneumonia	2 g 8 hourly IVI	
Meningococcal Meningitis	2 g 8 hourly IVI for 7 days	
Pnemococcal Meningitis	2 g 8 hourly IVI for 10 days	
Haemophilus Influenza	2 g 8 hourly IVI for 10 days	
Paediatric		
Severe Infections	20mg-40mg/kg/dose 8 hourly (max 2g)	
Meningitis	40mg/kg 8 hourly	

Appendix D: General Data Collection Tool – modified from South African Antibiotic Stewardship Programme (SAASP)

Study number					
Age		**Sex**		**Ward**	
Diagnosis		Pneumonia			
		Meningitis			
		Central line infection			
		Intra-abdominal infection			
		Cellulitis			
		Urinary tract infection			
		Other (Please Specify):			
Source		Hospital Acquired		Community Acquired	
Indication		Prophylactic			
		Empirical			
		Definitive			
		MDR Pathogen			
Cultures		Sent before antibiotic administered			
		Sent after antibiotic administered			
		Not sent			
		Microorganism - if identified:			

Prescribing Criteria	Drug name	Meropenem		
	Dosing Frequency			
	Duration of treatment			
Other	Co-administration with other antibiotics?		If yes, which antibiotic?	
	Adverse drug reaction present?		If yes, what type of ADR?	

Appendix E: Ethics approval obtained from the National Health Research Database (NHRD).

health
Department:
Health
North West Provincial Government
REPUBLIC OF SOUTH AFRICA

2030 NDP

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Private Bag X 2068
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RESEARCH, MONITORING & EVALUATION

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HEAD OF DEPARTMENT
2022 -11- 15
NORTH WEST DEPARTMENT OF HEALTH
PRIVATE BAG X 2068, MMABATHO, 2735

Name of Researcher: **Ms S. Mohun**
University of the Witwatersrand

Physical Address: _____
(Work/ Institution) _____

Subject: **Research Approval Letter – A retrospective review on the utilisation of meropenem in a tertiary hospital setting.**

This letter serves to inform the Researcher that permission to undertake the above-mentioned study has been granted by the North West Department of Health. The Researcher must arrange in advance a courtesy meeting with the District Chief Director and the Chairperson of the District Health Research Committee (DHRC) (as per their details below), to introduce their research team/members on the proposed research to be undertaken. The researcher can thereafter proceed to the identified institution/s and/or facility and produce this letter to the Management as proof that the research was approved by the NWDoH.

This letter of permission should be signed and a copy returned to the department. By signing, the Researcher agrees, binds him/herself and undertakes to furnish the Department with an electronic copy of the final research report. Alternatively, the Researcher can also provide the Department with an electronic summary highlighting recommendations that will assist the Department in its planning to improve some of its services where possible. Through this, the Researcher will not only contribute to the academic body of knowledge but also contributes towards the bettering of health care services and thus the overall health of citizens in the North West Province.

Below are the contact details.

Office of the Chief Director: Bojanala District	**Chairperson of the DHRC**
Dr K. Segwai	Prof. J. Tumbo
Contact person: Goitsemang Khumalo	**Contact person:** Obakeng Masango
014 592 8906 KhumaloG@nwpg.gov.za	014 592 8906

Kindest regards,

Dr. FRM Reichel
Director: RM&E

Researcher

Appendix F: Human Research Ethics Committee – Medical approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Miss Shameeda Mohun

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M220537

NAME: (Principal Investigator)	Miss Shameeda Mohun
DEPARTMENT:	Pharmacy and Pharmacology Job Shimankana Tabane Hospital, Rustenburg, North West
PROJECT TITLE:	A retrospective review on the utilisation of meropenem in a tertiary hospital setting
DATE CONSIDERED:	27/05/2022
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Mrs R. Shaikh
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	29/09/2022

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions.Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **May** and will therefore be due in the month of **May** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix G: Approval from NHLS to access database

Academic Affairs and Research
1 Modderfontein Road, Sandringham, 2031
Tel: +27 (0)11 555 0367/0406
Email: babatyi.kgokong@nhls.ac.za
academic.research@nhls.ac.za
Web: www.nhls.ac.za

15 September 2022

Applicant: Shameeda Mohun
Institution: University of the Witwatersrand
E-mail Address: shameeda.mohun@gmail.com
Tel: 014 538 2562 **Cell:** 064 681 0102

CC: Tuelo Nteta, Rubina Shaikn

Project Title: A retrospective review on the utilisation of meropenem in a tertiary hospital setting
Reference Number: PR2227125

Research Application Type(s):
1. Request for Data

RE: APPROVAL LETTER: REQUEST TO ACCESS NHLS RESOURCES FOR RESEARCH PURPOSES

This letter serves to advise that the application requesting permission to conduct the above-mentioned research using the listed NHLS resources has been reviewed and **"Approved"**. Please note that the approval is granted on the condition that you comply with the NHLS Research Material and Data Access Policy and requirements stated below.

1. All material and data requested shall be used as per the research protocol submitted to the NHLS and as approved by the relevant Health Research Ethics Committee (HREC) in South Africa.
2. Access to the NHLS material and/or data shall be limited to the minimum required for successful completion of the approved study and shall be made available ***without patient names***.
3. Confidentiality shall be maintained at the participant and institutional level and there shall be no disclosure of personal information or confidential information.
4. The material and/or data obtained from the NHLS shall be anonymised and not, for any reason, be used to track or recruit patients as no pre-approval/consent is obtained from patients.
5. Processes shall be discussed with the relevant NHLS departments (i.e. Corporate Data Warehouse (CDW), NHLS Laboratory Management, Operations Office, etc.) and agreed upon.
6. Any amendments to the study requirements, including the use of the material and/or data for purposes not initially disclosed to the NHLS) shall be cleared by an approved HREC and submitted to the NHLS for approval via the AARMS system – https://aarms.nhls.ac.za.
7. The NHLS shall be acknowledged as a source of material and/or data in any output, such as abstracts and journal articles, emanating from the project.
8. A final report of the research study and any published output resulting from this study shall be submitted to the NHLS via AARMS

Please note that this letter constitutes approval by the NHLS Academic Affairs and Research Office. The NHLS entities tasked with providing the material and/data may have additional requirements for access. Data related queries may be directed to NHLS CDW, email: zarina.sabat@nhls.ac.za; contact number: 011 386 6074 and sample related queries (if applicable) shall be directed to the relevant business manager.

Dr Babatyi Malope-Kgokong
National Manager: Academic Affairs and Research

Appendix H: Plagiarism Declaration

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

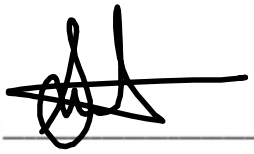
PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

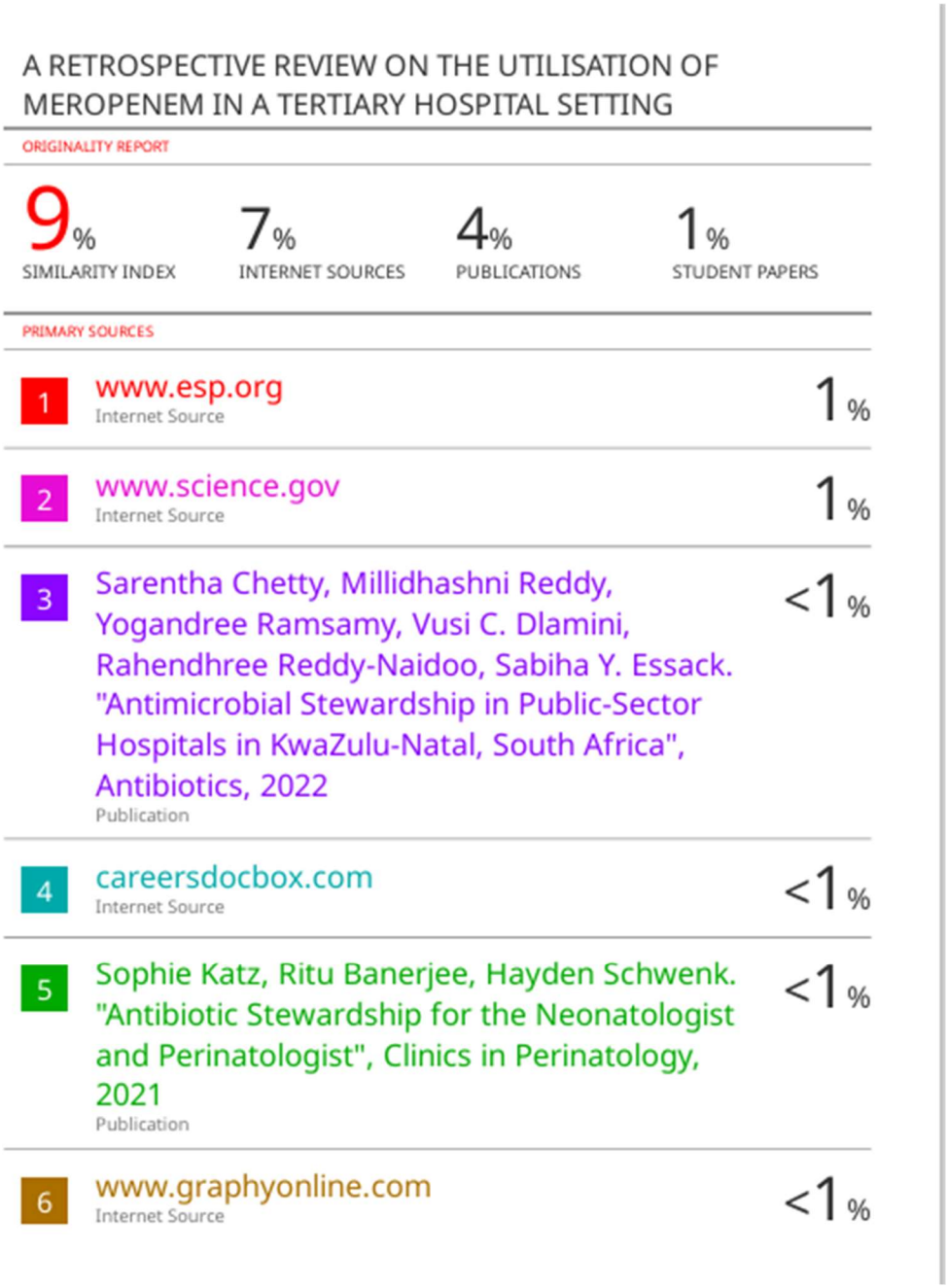
I Shameeda Mohun (Student number: 712 746) am a student registered for the degree of Masters of Medicine (Clinical Pharmacy) in the academic year 2023.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature:  Date: 05 June 2024

Appendix I: Turn It In Plagiarism Report



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