MEROPENEM UTILIZATION, ANTIMICROBIAL RESISTANCE PATTERNS AND FACTORS INFLUENCING MEROPENEM PRESCRIBING AND ADHERENCE TO GUIDELINES BY CLINICIANS AT KENYATTA NATIONAL HOSPITAL, KENYA

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A Thesis Submitted in Partial Fulfillment of the Requirements for the degree of Master in Pharmacoepidemiology and Pharmacovigilance in the Department of Pharmacology and Pharmacognosy in the University of Nairobi

DECLARATION

This thesis is my original work and has not been presented for a degree in any other university

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DEDICATION

I dedicate this work to my beloved parents and siblings for their unending love and support throughout my career and to my beloved fiancée for always believing in my potential and reminding me that I have what it takes to succeed.

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LIST OF ABBREVIATIONS

AMR	Antimicrobial Resistance
CMA	Centered Moving Averages
CSF	Cerebrospinal Fluid
CST	Culture and Sensitivity Test
DHP-1	Dehydropeptidase-1
ESBLs	Extended Spectrum Beta-Lactamase enzymes
GCP	Good Clinical Practices
ICU	Intensive Care Unit
ID	Infectious Disease
IV	Intravenous
KNH	Kenyatta National Hospital
KNH/UoN ERC	Kenyatta National Hospital /University of Nairobi Ethics and Research Committee
KPC-Kp	*Klebsiella pneumonia* carbapenemase-producing *Klebsiella pneumoniae*
MA	Moving Average
MIC	Minimum Inhibitory Concentrations
MUR	Medication Use Review
NMTC	National Medicine and Therapeutic Committee
PE	Pharmacoepidemiology

OPERATIONAL DEFINITIONS

Antibiotics: Are substances produced by or derived from certain fungi, bacteria, and other organisms, that can destroy or inhibit the growth of other microorganisms. In this study, the term antibiotic is used as a synonym for drugs used to treat bacterial infections in both people and animals.

Antimicrobial agent: This is an agent that either kills or slows the growth of microbes. In this study, it referred to antibiotics and in particular meropenem.

Antimicrobial resistance: Is the ability of a microorganism to stop an antimicrobial agent such as an antibiotic from working against it.

Clinician/prescriber: Is a healthcare professional who works as a primary caregiver of a patient in a healthcare facility or patient's home. In this study, the term refers to a registered medical officer and a medical specialist (consultant).

Drug utilization research: This is the marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences.

Drug use problem: Any error that can occur during the medication use cycle

Empiric therapy: Is drug selection purely based on clinician's experience and relevant clinical observation and knowledge of current resistance patterns in suspected pathogens

Indicators of drug use: Are the objective measures that describe the drug use situation in a health facility

Medical consultant: Medical doctor who has completed specialized medical training and place in the specialist register in his/her field of specialization

Prescription: A written order from a prescriber to a dispenser for the preparation and dispensing of a drug to a patient

Prescribing practice Is the frequency of choice to prescribe a certain drug from a pool of drugs that could be used in its stead to treat an infection

Rational drug use: This means that patients receive medications appropriate to their clinical needs, in doses that meet their requirements, for an adequate period and at the lowest cost to them and their community.

ABSTRACT

Background: In hospitalized patients, antibiotics are the most commonly prescribed drugs. The rising level of antibiotic resistance, caused by frequent and inappropriate use of antimicrobial agents, is a major concern of health care systems throughout the world. Meropenem is a second-generation carbapenem with a broad spectrum of activity against a majority of gram-positive, gram-negative and anaerobic bacteria, hence it is prone to misuse. and this raises concerns about the emergence of antimicrobial resistance in Kenya and beyond.

Objectives: The main objective was to describe meropenem utilization, antimicrobial resistance patterns and factors that influence meropenem prescribing by clinicians at Kenyatta National Hospital.

Methods: The study was conducted in two parts at Kenyatta National Hospital. The first was a descriptive quantitative retrospective study describing meropenem utilization patterns for the period between January 2016 and December 2017. Patient files were reviewed. The second part was a cross-sectional study on meropenem prescribing practices by clinicians by use of a self-administered questionnaire. Convenient sampling was applied. All the abstracted data were subjected to descriptive data analysis. Inferential data analysis was carried out and a chi-square test was used. The level of significance was set at 0.05. Data analysis was done using SPSS version 20 software. Approval to carry out this study was granted by Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (KNH/UoN-ERC)

Results: A total of 452 medical records of patients on meropenem were reviewed. Meningitis 45 (27.6%) was the major indication in children aged 12 years and below while soft tissue infection, 75 (26%) was the major indication in patients aged 13 years and above. 134 (82.2%) children received the optimal dose. Meropenem was used as empirical therapy in 348 (77%) of the patients. Gram-negative bacteria were the major isolates, (97.6%) and resistance was high with *Acinetobacter baumannii* 9 (90.0%). A total of 39 clinicians were interviewed of whom 20 (51.3%) were females. There was a statistically significant association between specialization and meropenem prescribing practices (p value=0.04). Most clinicians, 22 (56.4%) relied on the advice of an infectious disease specialist before prescribing meropenem.

Conclusion: This study has shown that meropenem was mainly used empirically. Continuous medical education, functional drug therapeutic committees and regular drug use research programs remain important aspects in promoting rational antimicrobial use.

1.0: CHAPTER ONE: INTRODUCTION

1.1: Background

Antibiotics are the most commonly prescribed drugs in hospitalized patients whereby, more than a third of the patients receive an antimicrobial treatment (1). Increasing antibiotic resistance is one of the major concerns of health care systems throughout the world. Several factors are responsible for the emergence of this problem of which, frequent and inappropriate use of antimicrobial agents play an important role (2).

Meropenem is a second-generation carbapenem with a broad spectrum of activity. It is active against a majority of gram-positive, negative, and anaerobic bacteria. Thus, it is prone to misuse and this raises concerns about the emergence of antimicrobial resistance to this agent in Kenya and beyond. Meropenem is available as a powder for injection.

Broad-spectrum antibiotics such as carbapenems are essential for the empiric treatment of severe nosocomial infections. Empiric therapy is defined as drug selection purely based on the clinician's experience, relevant clinical observation, and knowledge of current resistance patterns in suspected pathogens (3). Concerns about increasing rates of multi-drug resistance to broad-spectrum antimicrobial agents have forced most researchers to evaluate the pattern of administration of these drugs worldwide (4).

Microbial resistance to meropenem is a rising worldwide public health problem in both hospital and community-acquired infections. Antimicrobial-resistant bacteria have negative impacts on treatment outcomes such as increased morbidity, prolonged hospital stay, and increased risk of mortality. In addition, patients infected with drug-resistant bacteria require more expensive therapy. Resistance to meropenem and other antimicrobials is a huge challenge in low-income countries because of the high prevalence of infection, irrational uses of antimicrobials, and lack of clinical microbiology laboratories for antimicrobial susceptibility testing (5).

Repression of meropenem resistance requires a change in the prescribing practices of clinicians. This change demands changes in their behavior towards the magnitude of the meropenem resistance problem. Therefore, information on clinicians' knowledge and beliefs on meropenem resistance will permit the development of more effective interventions on containment of the rising resistance. In the United States of America and

Europe, several surveys have been conducted to assess clinicians' knowledge and beliefs about antimicrobial use and resistance (6). However, these results may not necessarily apply to the situations in low- and middle-income countries like Kenya.

1.2: Problem Statement

Excessive and inappropriate use of antibiotics is a major factor in the emergence and spread of antibiotic-resistant bacteria (7). Prescribing antibiotics without a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Therefore, optimization of antibiotic use reduces the development of antibiotic resistance leading to lower healthcare costs by providing cost-effective treatments. Meropenem is considered to be a potent drug for the treatment of multi-drug resistant gram-negative infections. This is due to its stability against most of the beta-lactamases and high rate of permeation through bacterial outer membranes. However, a recent study has indicated the emergence of meropenem-resistant *Klebsiella pneumoniae* (8).

There is increased use of carbapenems in the hospitals, some of which may not be warranted or do not meet the national guidelines on the use of antibiotics in the management of bacterial infections. A study conducted on meropenem utilization in patients in the intensive care unit (ICU) in a hospital in Sudan showed that meropenem was prescribed for all patients without culture and sensitivity reports (9). From that study, meropenem was used empirically in 80% of the patients while only 12.6% were indicated for sepsis and 7.4% for pneumonia.

Resistance to meropenem and other antimicrobials is challenging in Kenya due to the high prevalence of infections, irrational use of meropenem and other antimicrobials, and inadequate antimicrobial susceptibility testing. To overcome meropenem resistance, there is a need for a change in the prescribing practices of clinicians. The information on clinicians' knowledge and beliefs on meropenem resistance will aid in the development of more effective interventions to control the rising resistance.

1.3: Research Questions

1. What are the prescribing patterns of meropenem at Kenyatta National Hospital?
2. What are the microbial resistance patterns to meropenem at Kenyatta National Hospital?
3. What are the factors that influence clinicians to prescribe meropenem?
4. What is the rate of meropenem consumption at Kenyatta National Hospital for the period 2016 to 2017?

1.4: Research Objectives

1.4.1: Main objective

To describe meropenem utilization, microbial resistance patterns and factors that influence meropenem prescribing and adherence to guidelines by clinicians at Kenyatta National Hospital.

1.4.2: Specific objectives

1. To describe the prescribing patterns of meropenem at Kenyatta National Hospital for the period 2016 to 2017.
2. To describe the microbial resistance patterns to meropenem at Kenyatta National Hospital for the period 2016 to 2017.
3. To identify the factors that influence clinicians to prescribe meropenem.
4. To describe the rates of meropenem consumption at Kenyatta National Hospital for the period 2016 to 2017.

1.5: Study Justification

The rising emergence of meropenem-resistant bacteria and the slower rate of development of new antibiotics are critical problems (10). Studies conducted in different hospitals in other parts of the world showed that in most of the cases, meropenem was prescribed empirically, hence there was a need for a local study to evaluate its use (9,11,12). There were no studies in east Africa that had evaluated meropenem use in public facilities. the contextual factors that influence its use had not been evaluated. This research has evaluated meropenem use in a public tertiary teaching hospital.

This study has provided data on meropenem use and adherence to prescribing guidelines at KNH. This data is important for the antimicrobial stewardship team as it has identified

gaps, such as empiric therapy, dosing errors among others, in the use of meropenem and can help in designing interventions to promote its rational use. This would in turn lead to reduced resistance to carbapenems and related drugs which are currently reserve drugs for the management of severe drug-resistant infections in hospitalized patients.

The findings of this study can also be used to advocate for antibiotic therapy monitoring because drug use monitoring is currently not routinely conducted in Kenya and other East African countries.

1.6: Conceptual Framework

The rational use of meropenem was described based on interrelating planning models in three phases. It integrates with observed, contextual information and lessons learned in practice (13). Prescribing behavior is influenced by predisposing, reinforcing and enabling factors. These would include: knowledge, attitudes, beliefs, and personality traits. Others are peer pressure, drug promotion, prescribers' diagnostic skills, and exposure to hospital formulary and guidelines. These guidelines would encompass the practice of culture and sensitivity testing. The conceptual map is shown in Figure 2.2.

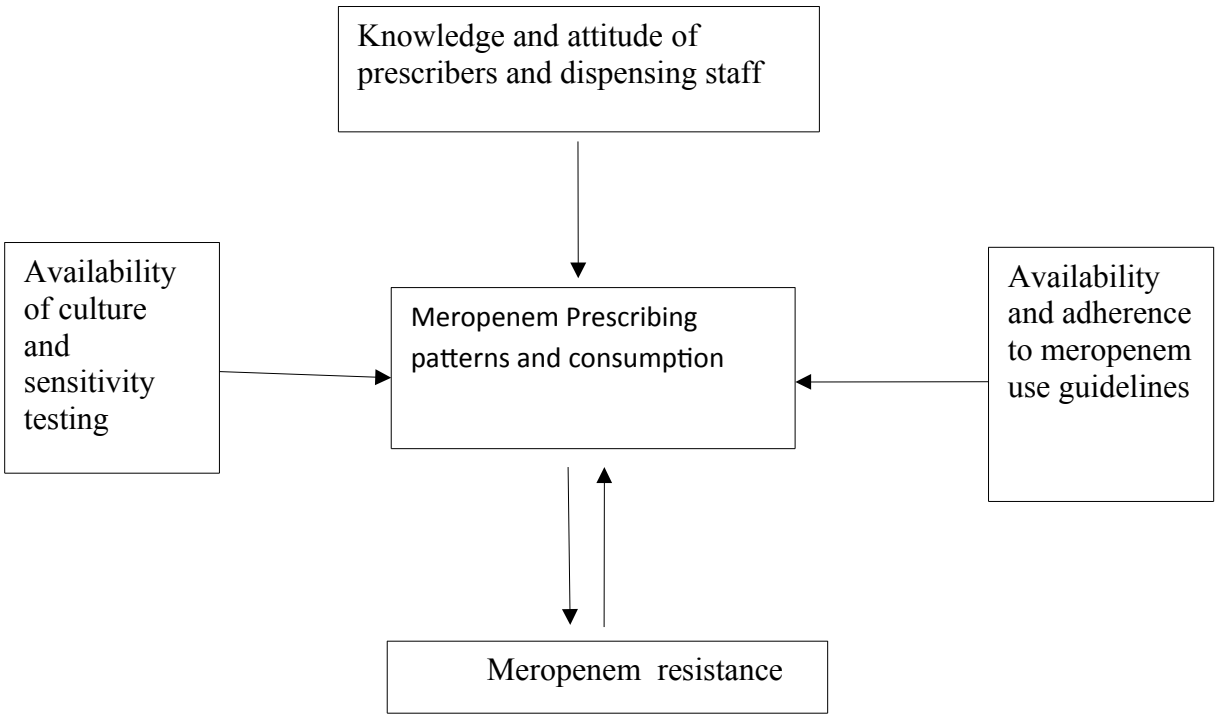

Figure 1.1: Conceptual framework for rational meropenem use

2.0: CHAPTER TWO: LITERATURE REVIEW

2.1 Meropenem Use

The initial clinical experience with carbapenems indicated that they could provide a breakthrough in the treatment of severe infections in infants and children. Meropenem has undergone extensive investigation in most parts of the world and appears to be promising in the treatment of moderate to serious infections (14).

Meropenem is a second-generation carbapenem with a broad spectrum of activity against both gram-positive and gram-negative bacteria (15). It acts by inhibiting bacterial cell wall synthesis by penetrating cell walls and binding to penicillin-binding protein targets (15).

Meropenem is relatively stable to hydrolysis by dehydropeptidase-1 (DHP-1) compared to imipenem (14). When meropenem was compared with numerous single- and multiple-drug regimens consisting of second and third-generation cephalosporins (e.g., ceftazidime, ceftriaxone, cefotaxime, and cefoxitin), gentamicin and other aminoglycosides, piperacillin, clindamycin, ciprofloxacin, and/or metronidazole, it consistently demonstrated a broader spectrum of activity and was generally found to be more potent (16,17). Meropenem is a restricted, broad-spectrum and costly antibiotic (18). The main results of irrational use of restricted antibiotics are increased drug resistance and expenditure. Thus, use must be monitored closely to promote adherence to standard treatment guidelines.

2.2: Indications of Meropenem

Meropenem for injection is normally indicated for the treatment of complicated appendicitis and peritonitis caused by viridans group streptococci, *Klebsiella pneumoniae, Bacteroides fragilis, B. thetaiotaomicron*, and *Peptostreptococcus species (18).* Meropenem is also indicated for the treatment of bacterial meningitis caused by *Haemophilus influenzae, Neisseria meningitidis*, and penicillin-susceptible isolates of *Streptococcus pneumoniae*. It is effective in eliminating concurrent bacteremia associated with bacterial meningitis (19). It is also indicated for the treatment of complicated skin infections due to *Streptococcus aureus, Streptococcus pyogens, Enterococcus foecalis* and, *Pseudomonas aeruginosa, Escherichia coli, Proteus mirabilis* and *Peptostreptococcus* species (19).

2.3: Factors Affecting Meropenem Use

There are several determinants of meropenem use. Some of these factors are age, gender, occupation, disease condition, type of ward of admission, and culture and sensitivity results. Other factors include: the effectiveness of infection prevention and control measures, availability of hospital's hygiene practices, the efficiency of the microbiology laboratory and dissemination of results, appropriate prescribing of antibiotics, use of policies and Standard Treatment Guidelines, stock management of essential medicines and consumables and Pharmacist's clinical monitoring of meropenem use (20).

2.4: Prescribing Patterns of Meropenem

2.4.1: Administration of meropenem

Meropenem has two dosing regimens. One option is prolonged infusion time and the second one is the small dose short interval regimen. Prolonged infusion time involves increasing the administration time of Meropenem from 30 minutes to 2-4 hours (21). The small dose short interval regimen involves administration of 500mg every 6 hours instead of 1g every 8 hours. Three studies compared these dosing strategies and their effect on clinical endpoints (22, 23,24).

There were no significant differences in the clinical success rates between the two dosing regimens (23). A historical cohort study by Patel et al (2005), showed that the traditional and alternative regimens had comparable efficacy in terms of clinical success (91% vs 92%) and hospital mortality (8% and 11%, p=0.24) respectively.

2.4.2: Meropenem use in adults with impaired renal function

Meropenem is predominantly excreted unchanged via urine. Therefore, in patients with impaired renal function, the dosage should be reduced as presented in Table 1.

Table 2.*1*: Schedule for administration of meropenem (25)

Creatinine clearance (ml/min)	Dose (based on unit doses of 500mg, 1g, 2g)	Frequency
26-50	One unit dose	Every 12 hours
10-25	One-half unit dose	Every 12 hours
<10	One-half unit dose	Every 24 hours

Meropenem is cleared by hemodialysis and haemofiltration. Thus, the unit dose should be administered at the end of the procedure if continued meropenem use is necessary (25).

2.4.3: Indicators of rational use of meropenem

Indicators of drug use are defined as the objective measures that describe the drug use situation in a health facility (26). They are used to assess potential problems in drug use, prioritize and focus efforts to correct these problems. Some of the indicators/aspects measured in meropenem use studies include prescribing patterns (empirical or directed therapy), duration of treatment, culture and antimicrobial susceptibility report, dose adjustment in renal failure and treatment outcomes (27). This ensures that clinicians use the appropriate medicine to patients for their clinical condition, in doses optimized for their individual needs, over an appropriate duration and at the lowest cost to patients and the community (26). The main outcomes to be measured should include but not be limited to indication, dose interval and duration of treatment and creatinine clearance (18).

2.4.4: Problems with meropenem use

The major problem with the use of meropenem is empiric therapy (25). Empiric therapy is defined as drug selection purely based on the clinician's experience, relevant clinical observation and knowledge of current resistance patterns in suspected pathogens (28). A study conducted in Sudan reported that clinicians used meropenem in all ICU patients without determining their exact infections (9). The prevalence of empiric use of meropenem was highest in Tehran (85.9%), Sudan (80%), and France (60%) whereas it was lowest in Iran (21-46.7%) (1,9,18,29).

2.5: Microbial Resistance Patterns to Meropenem

Persistence microbial resistance to antibiotics poses a severe threat to human life (30). Increased use of carbapenems in the hospital environment can cause more selective pressure on hospital microbiota, thus enhancing the subpopulation of microorganisms with increased resistance to these antibiotics (31). Antimicrobial surveillance programs in Latin America showed that Acinetobacter species and Pseudomonas aeruginosa presented resistance of 18.17% and 35.6% to meropenem respectively (32,33). In pseudomonas species, resistance to meropenem is mediated via efflux pumps (34).

2.5.1: Lack of culture and sensitivity results

Antimicrobial culture and sensitivity test is conducted to identify causative pathogens and the antibiotics they are sensitive to. Guidelines for the treatment of bacterial infections highlight the importance of prompt antimicrobial treatment to save lives (35). Reduction in mortality is realized when antimicrobials are initiated within the first hour of diagnosis, thereafter, culture-guided treatment should be performed (36). Most meropenem prescription anomalies range from its use with inadequate culture and sensitivity tests and lack of dose adjustment in renal failure (6).

2.6: Clinicians' knowledge, attitudes and practices of prescribing meropenem and their perceptions of causes of meropenem resistance

General understanding of the knowledge, attitude and practices of clinicians towards antibiotic resistance is key to developing interventions that would aid in behavioral change in prescribing.

2.6.1: Kenyatta National Hospital guide for meropenem therapy

The guideline was developed to ensure rational antibiotic use. It was developed through a concerted effort of a multi-disciplinary team composed of infection, prevention and control (IPC) specialists, microbiologists, pharmacists and medical consultants. It stratifies patients into four categories (37). Meropenem was majorly to be used for patients under category three who had a long hospital stay, invasive procedures, advanced immunosuppression, neutropenia and had recent and multiple antibiotic therapies (37). It recommends the use of meropenem in patients with infections due to gram-negative bacteria such as: *Acinetobacter, Pseudomonas, Klebsiella pneumoniae, E. coli, Citrobacter and Enterobacter species* which are the common pathogens in patients under category 3.

2.6.2: Compliance to guidelines on meropenem prescribing

In the advent of increasing resistance and paucity of new drug development, there is a growing need to enhance the rational use of antibiotics. A guideline provides the foundations for rational use of antibiotics to counteract the increasing resistance and improve the quality of care for patients by maximizing clinical outcomes and minimizing toxicity (38).

Based on the existing guidelines, previous studies have indicated that 21-46.5% of meropenem prescriptions were inappropriate (18, 28, 35, 39). To enhance the appropriate use of reserve antibiotics such as meropenem, it is prudent to follow the existing meropenem use guidelines. A study in Iran showed that clinicians sought the advice of an Infectious Disease specialist while prescribing meropenem only for 52% of the patients (7) which was part of their meropenem use guidelines. Compliance to treatment was yet to be achieved in Sudan (20) while the dosages were inappropriate in 7.3% of patients treated with antibiotics in Turkey (1).

The findings of this study can be used to advocate for antibiotic therapy monitoring because drug use monitoring is currently not routinely conducted in Kenya and other East African countries.

3.0: CHAPTER THREE: METHODOLOGY

This study was conducted in two parts. The first part was a descriptive quantitative retrospective study that described meropenem utilization for two years (1st January 2016-31st December 2017). The second part was a cross-sectional study that aimed at identifying contextual factors that influence meropenem use.

3.1: Part 1: Quantitative retrospective study on meropenem utilization

3.1.1: Study design

The study design for the part I was a descriptive quantitative retrospective design whereby, patient files for the period between 1st January 2016 to 31st December 2017 were retrieved and analyzed. The data collection was done from June 2018 to August 2018.

3.1.2: Study site

The study was conducted at the inpatient department (medical pediatric, renal and ICU wards) of Kenyatta National hospital which is the largest teaching and referral public hospital in Kenya. It is located along Hospital Road in the Upper Hill region of Nairobi city. It caters to all medical requirements for the people of Nairobi, surrounding areas and East Africa at large. The outpatient department consists of the Accident and Emergency department and specialty clinics for chronic cases. KNH has a bed capacity of 1800.

Kenyatta National Hospital was selected because it has a large turnover of patients with various infections and has a wide range of specialized clinics hence it would enable the attainment of a sufficient sample size. It is also the largest regional tertiary and university teaching hospital hence, understanding the clinical practices in the facility in regards to meropenem use would influence its use patterns in other facilities in Kenya.

3.1.3: Study Population

The study population comprised of pediatric and adult patients hospitalized at Kenyatta National Hospital between 1st January 2016 and 31st December 2017.

3.1.4: Eligibility Criteria

3.1.4.1: Inclusion and exclusion criteria

Patients were included in the study if they were admitted in the various wards (medical, surgical, pediatric) had been treated with meropenem and their records were retrievable for the period between 1st January 2016 and 31st December 2017. Patients were excluded from the study if they had no meropenem in their treatment sheets.

3.1.5: Sample Size

A study in Iran reported the prevalence of meropenem use as 22% (7). Therefore, using this prevalence, the Cochran formula was used to determine the sample size for this study.

$N=z^2pq/e^2$

Where: N=desired sample size

z=z statistic for 95% confidence interval which is 1.96

p=estimated proportion of outcome of interest (assumed prevalence of 22%)

q=1-p

e=acceptable margin of error set at 5% for proportion being estimated

Therefore, $N=1.96^2\{0.22(1-0.22)/0.05^2$

$=263$

This figure was inflated by 72% to cater for records with missing data, make the study robust and improve on validity and reliability. The sample size was 452.

3.1.6: Retrieval and selection of cases

The sampling frame consisting of a list of records of meropenem dispensed to the wards between 1st January 2016 and 31st December 2017 was obtained from the pharmacy database. A total of 800 patient records with patients' names and registration numbers were retrieved. About 120 duplicated patient records were removed from the list after which the list was printed and taken to the KNH records department to be used in searching for patient files. A further 130 records were excluded due to a lack of patient file numbers. Only 550 patient files could be retrieved and screened for eligibility after which 98 records without meropenem prescriptions were excluded. Finally, only 452 patient files with meropenem prescriptions in their records were included in the study.

The sampling flow chart is as shown in Figure 3.1.

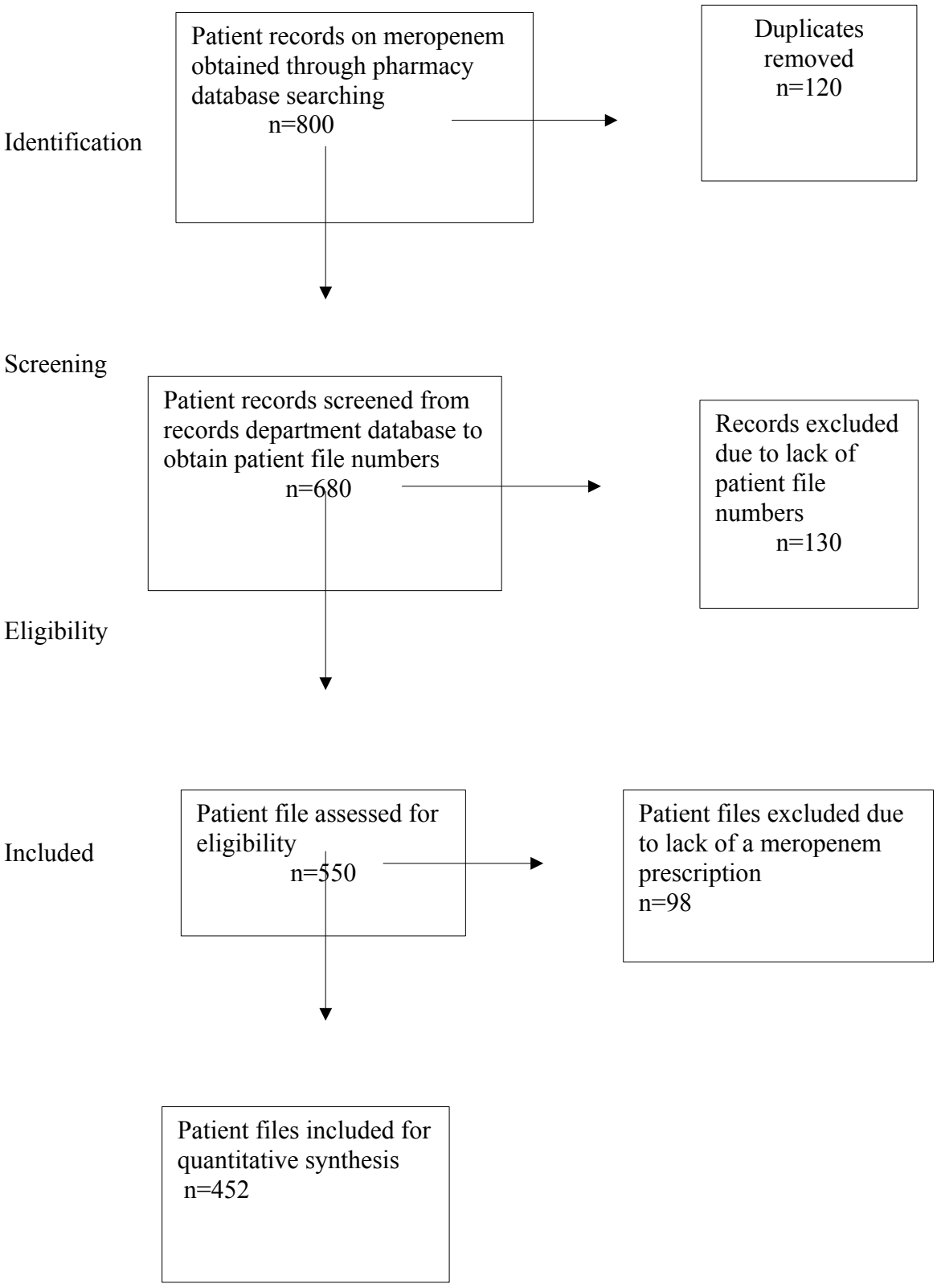

Figure 3.1: Flow chart for sampling of patient records to be included in the study.

3.1.7: Data Collection

Data collection was done between June 2018 and August 2018 from the following areas: from patient records to obtain clinical data, from the pharmacy procurement department to obtain meropenem consumption data and from archived laboratory records for the period between 1st January 2016 and 31st December 2017 to obtain resistance data. Patient files were reviewed and data on socio-demographic characteristics, indications for meropenem and the prescribing patterns were abstracted and entered in a pre-designed data abstraction tool. Data on resistance patterns were also abstracted from the culture and sensitivity reports which were in the patient files. This was done for both children and adult patients.

General meropenem resistance data for *Klebsiella pneumoniae, Pseudomonas aeruginosa, Escherichia coli* and *Acinetobacter baumannii* was obtained from the Kenyatta National Hospital archived laboratory data for the period between 1st January 2016 and 31st December 2017. This data showed the total isolates that were cultured for meropenem.

Meropenem consumption data at KNH was obtained from the pharmacy stores. Records of meropenem issued from the main store to the various dispensing areas within KNH were reviewed. The total amount of meropenem issued was computed in terms of milligrams.

3.1.8: Variables and definitions

3.1.8.1: Irrational meropenem use

This is when patients receive meropenem inappropriate to their clinical needs, in doses that do not meet their requirement for an inadequate period, lack of culture and sensitivity test and lack of/inappropriate monitoring of therapy (41).

3.1.8.2: Correct dosage

Refers to the right quantity of medicine prescribed to be taken at a given time depending on age, weight, body surface area and severity of the infection (41). In this study, correct dosage meant meropenem administered 500-1000mg and 10-40mg/kg in adults and children respectively (23).

3.1.8.3: Correct dosing frequency

It refers to the duration between dose administrations of meropenem. In this study, it was when the patient was given the medicine 8 hourly or 12 hourly (37).

3.1.8.4: Adequate duration

Refers to when meropenem was administered to a patient for a period between 5 days-14 days. Duration of more than 14 days was prolonged use. In this study, adequate duration meant meropenem was administered for 5-14 days (37).

3.1.8.5: Success

This was defined as the eradication of infection and avoidance of resistance (42). This was determined by the recession of symptoms and discharge.

3.1.9: Data Management and Quality Assurance

All data obtained from patient prescriptions were double-checked by the researcher during data entry. The collected data were entered by the researcher into Epi Info version 7 software. The data were backed up by the researcher upon new entry. The system was password protected and the final report was subjected to inspection and audit according to good clinical practices (GCP) standards and protocols.

3.1.10: Data Analysis

All the data were subjected to descriptive data analysis. The continuous variables were summarized as the means, standard deviations and medians and interquartile ranges. Categorical variables were summarized as frequencies and percentages. The analyzed data were then presented in the form of tables, figures and graphs.

Inferential data analysis was then carried out to describe the patterns of meropenem use. The chi-square test was used to determine whether there were associations between variables. The level of significance was set at 0.05. Data analysis was done using SPSS version 21 software. Meropenem consumption data was computed quarterly. Four moving averages were then computed and a time series plot was generated. This was aimed at illustrating the trend of meropenem consumption over the years.

3.2: Part II: Study on meropenem prescribing practices

3.2.1: Study design

A cross-sectional survey of clinicians prescribing meropenem between 1st June 2018 and 31st August 2018 was conducted.

3.2.2: Study site

The study was carried out at Kenyatta National Hospital at the clinicians' offices and wards.

3.2.3: Study population

The study population was selected from clinicians practicing at KNH.

3.2.4: Eligibility of clinicians

A clinician was included in the study if he/she was a medical consultant or a medical postgraduate trainee working at KNH, had worked in the wards for at least 6 months and he/she had provided informed consent. Those who did not meet this criterion were excluded.

3.2.5: Sampling

Convenient sampling was applied because the expected number of prescribers at the site of the study was expected to be less than 30.

3.2.6: Recruitment and Consenting Process of Clinicians

A list of clinicians, working in the levels of expertise at the departments of medicine, surgery, pediatrics, obstetrics and gynecology, and their telephone contacts obtained from the nurse in charge of wards at KNH. The clinicians were approached using two methods. After a major ward round, at least three to five clinicians were approached individually and asked to suggest a time and a date when the details of the study could be explained to them. Alternatively, they were called and requested to select a date and time when the details of the study could be explained to them. At the convenience of the clinician, the purpose of the study, procedures, benefits and rights of the clinician was explained with the aid of the informed consent form. Those who gave informed consent were recruited into the study. The consent form can be found in Appendix D.

3.2.7: Data collection

After provision and signing the consent form, the structured questionnaires were issued to the clinicians for self-administration. However, some clinicians requested the researcher to conduct the interviews on them and fill the questionnaire on their behalf. The structured questionnaire was designed to collect information on bio-data and the factors that influenced clinicians in prescribing meropenem. The data collection form appears in appendix E.

3.2.8: Variables

The variables that were to be collected are as presented in Table 3.2.

Table 3.2: Factors influencing meropenem prescribing at Kenyatta National Hospital

Intrapersonal and interpersonal variables	Institutional variables	Policy variables
Percentage with knowledge of meropenem guidelines	Presence of CMEs	Availability of guidelines
Percentage of knowledge of meropenem resistance	Presence of antimicrobial stewardship team	Availability of meropenem sparing drugs
Percentage of those who know the strains that are resistant to meropenem	Availability of culture and sensitivity testing	Restriction on meropenem use
Percentage of influence from peers and medical representatives	Availability of meropenem sparing antibiotics	

3.2.9: Data analysis

The questions on beliefs used Likert-scale responses. At the end of the interview, the collected information was transcribed into a word document with a unique number for each participant. The responses were transcribed and coded numerically. The study data was analyzed using Statistical Package for Social Sciences version 21 software. Proportions were calculated for categorical variables while means and standard deviations were calculated for continuous variables. Inferential data analysis was then done where the

chi-square test was used to estimate associations between the independent and dependent variables. The level of significance was set at 0.05.

3.3: Ethical Considerations

The researcher obtained approval to carry out this study from Kenyatta National Hospital/ University of Nairobi Ethics and Research Committee (KNH/UoN-ERC) before the commencement of the study. The research approval number is P346/05/201. The approval letter is presented in appendix F. At the hospital level, approval was obtained from the hospital management through an official letter. Informed consent was obtained from prescribers of meropenem.

Confidentiality and privacy of patients' medical information: access to patients' data was limited to the researcher, locking up of folders, removing identifiers and encryption of information. The data instruments were stored in a password-protected database.

4.0: CHAPTER FOUR: RESULTS

This chapter is divided into two sections. The first section reports the findings of the quantitative retrospective study which described meropenem utilization while the second section reports the outcomes of the cross-sectional survey of clinicians to determine the factors that influence their meropenem prescribing practices. The first section is further subdivided into three parts. Part I describes meropenem use in hospitalized children aged 12 years and below. Part II describes meropenem use in hospitalized patients aged 13 years and above while part III describes meropenem microbial resistance data and meropenem consumption data.

4.1: Meropenem Utilization Patterns

A total of 452 hospitalized patients were sampled.

4.1.1: Section one part I: Meropenem use in hospitalized children aged 12 years and below

4.1.1.1: Demographic and baseline characteristics of children

A total of 163/452 (36.06%) children were aged 12 years and below of whom the majority were males 89 (54.6%). The majority of the children were aged below 5 years 144 (88.3%). Their median weight was 5.3kg with an IQR of 2.95-8.7. Most of the children were admitted to the pediatric wards, 150 (92%). The demographic and baseline characteristics were summarized as shown in Table 4.1.

Table 4.1: Characteristics of children on meropenem at Kenyatta National Hospital

Characteristic	n (%)
Gender	
Male	89 (54.6)
Female	74 (45.2)
Total	163 (100)
Age (years)	
0-28 days	52(31.9)
1 month-12 months	57 (35.0)
1.1-5 years	35 (21.5)
5.1-12 years	19 (11.7)
Total	163 (100)
Weight (kg)	
0-5	56 (34.4)
5.1-10	66 (40.5)
10.1-15	11 (6.7)
15.1-20	9 (5.5)
20.1-25	8 (4.9)
25.1-30	6 (3.7)
30.1-35	7 (4.3)
Total	163
Ward of admission	
Pediatric	150 (92.0)
Medical	6 (3.7)
Burns/surgical	7 (4.3)
Total	163

4.1.1.2: Indications for meropenem in hospitalized children aged 12 years and below

Most of the patients were diagnosed with meningitis 45 (27.6%), severe pneumonia 41 (22.2%) and neonatal sepsis 26 (16%). Other infections treated with meropenem were acute kidney injury 3 (1.2%) and febrile neutropenia 3 (1.8%). These indications are shown in Table 4.2.

Table 4.2: Main indications for meropenem in children aged 12 years and below at Kenyatta National Hospital

Indication	Number of children, n (%)
Bacterial meningitis	45 (27.6)
Severe pneumonia	41 (25.2)
Neonatal sepsis	26 (16.0)
Sepsis	18 (11.0)
Soft-tissue infections	14 (8.6)
Urinary tract infection	9 (5.5)
Intra-abdominal infection	6 (3.7)
Febrile neutropenia	4 (2.5)
Total	163

The indications were further categorized according to the age groups of the children as illustrated in Table 4.3. Neonatal sepsis 26 (16.0%) was the major indication in neonates. Severe pneumonia, 21 (12.9%) and bacterial meningitis, 20 (12.3%) were the main indications in patients between 1 month and 1 year. Patients aged between 1 year and 5 years, were mainly diagnosed with severe pneumonia 12 (7.6%) while those over 5 years were mainly diagnosed with soft tissue infections 7 (4.3%).

Table 4.3: Indications for meropenem by age group in children at Kenyatta National Hospital

	Number of children n(%)				
Indication	**0-28 days**	**1month-12 months**	**1.1-5 years**	**5.1-12 years**	**Total**
Bacterial meningitis	10 (6.1)	20 (12.3)	11 (6.7)	4 (2.5)	45
Severe pneumonia	6 (3.8)	21 (12.9)	11 (6.7)	3 (1.8)	41
Neonatal sepsis	26 (16.0)	0 (0)	0 (0)	0 (0)	26
Sepsis	0 (0)	11 (6.7)	6 (3.7)	1 (0.6)	18
Soft-tissue infections	2 (1.2)	1 (0.6)	4 (2.5)	7 (4.3)	14
Urinary tract infection	5 (3.1)	1 (0.6)	1 (0.6)	2 (1.2)	9
Intra-abdominal infection	1 (0.6)	1 (0.6)	2 (1.3)	2 (1.3)	6
Febrile neutropenia	1 (0.6)	3 (1.8)	0 (0.0)	0 (0.0)	4
Total	51	58	35	19	163

4.1.1.3: Meropenem prescribing patterns in hospitalized children

The dose of meropenem in pediatric patients was based on body weight. The recommended dose is 10-40 mg/kg body weight, intravenously 8-hourly. The dose that the patients received was categorized into three: those who received less than 10mg/kg body weight per dose were under dosed, 2 (1.2%), those who received 10-40 mg/kg body weight and therefore received the correct dose, 134 (82.2%) while those who received more than 40mg/kg body weight were overdosed, 20 (12.3%). The dosage was missing in 7 (4.3%) of the children. The dose distribution is as shown in Figure 4.1.

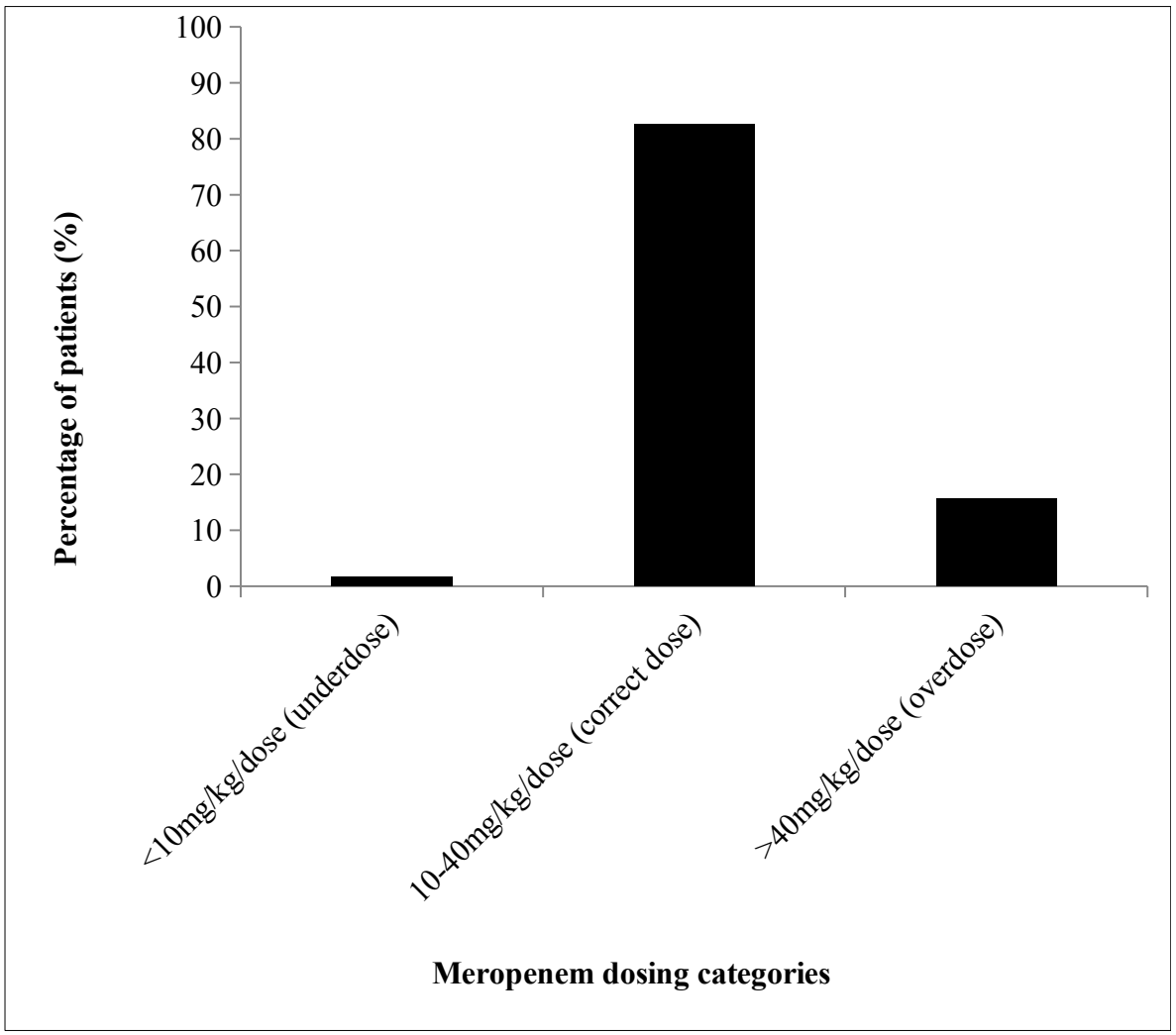

Figure 4.1: Meropenem dosing categories in children at Kenyatta National Hospital

4.1.1.4: Meropenem dose and duration of therapy in children

The correct dose was prescribed for 134 (82.2%) of the hospitalized children whereas 20 (12.3%) were overdosed. About 2 (1.2%) of the children were under dosed. Majority of the children received the 8 hourly doses, 139 (86.9%) while none got the 24-hourly doses. With regards to the duration of therapy, 39 (25.5%) of the patients received meropenem for less than 5 days while 114 (74.5%) received meropenem for 5-14 days. None had received prolonged meropenem therapy. Patients aged between 1 month and 1 year, 12 (7.8%) were mostly given meropenem for less than 5 days. The dose and duration of meropenem therapy are as shown in Table 4.4.

Table 4.4: Meropenem dose and duration of therapy of children at Kenyatta National Hospital

	Number of children n (%)				
	0-28 days	**1month-12 months**	**1.1-5years**	**5.1-12 years**	**Total**
Meropenem dose					
<10mg/kg/dose	0 (0)	1 (0.6)	1 (0.6)	0 (0)	2
10-40mg/kg/dose	45 (27.6)	48 (29.4)	31 (19)	10 (6.1)	134
>40mg/kg/dose	5 (3.1)	7 (4.3)	0(0)	8 (4.9)	20
Missing	2 (1.2)	1 (0.6)	3 (1.8)	1(0.6)	7
Total	52	57	35	19	163
Duration of therapy					
Less than 5 days	10 (6.5%)	12 (7.8%)	9 (5.9%)	8 (5.2%)	39
5-14 days	36 (23.5%)	39 (25.5%)	26 (17.0%)	13 (8.5%)	114
Missing	10				10
Total	56	51	35	21	163

There were no statistical differences between dose and frequency of administration across children's genders. The male children were more likely to be overdosed compared to the females (p=0.522).

4.1.2: Section one part II: Meropenem use in patients aged 13 years and above

4.1.2.1: Characteristics of patients aged 13 years and above

This group of patients comprised of 289/452 (63.9%) of the total study population of whom 140 (48.4%) were males and 149 (51.6%) were females. Majority of the patients were aged 19-30 years, 105 (36.3%) and most of them were from the medical wards, 219 (75.8%). The demographic characteristics of these patients are presented in Table 4.5.

Table 4.5: Characteristics of patients aged 13 years and above at Kenyatta National Hospital

	Number of patients	
Characteristics	**n**	**%**
Gender		
Male	140	48.4
Female	149	51.6
Total	289	100
Age (years)		
13-18	18	6.2
19-30	105	36.3
31-45	84	29.1
46-60	34	11.8
>60	48	16.6
Total	289	100
Ward of admission		
Medical	219	75.8
Burns/surgical	52	18
Renal	15	5.2
ICU	3	1
Total	289	100

4.1.2.2: Indications for meropenem in patients aged 13 years and above

The most common indication for meropenem was soft tissue infection, 75 (26.0%). The indications are as shown in Table 4.6.

Table 4.6: Indications for meropenem in patients aged 13 years and above at Kenyatta National Hospital

Indication	Number of patients, n (%)
Soft tissue infection	75 (26.0)
Severe pneumonia	57 (19.7)
Sepsis	54 (18.9)
Intra-abdominal infection	47 (16.3)
Urinary tract infection	29 (10.0)
Post-partum infection	15 (5.2)
Bacterial meningitis	12 (4.2)
Total	289

4.1.2.3: Meropenem prescribing patterns

For 286 (99.0%) patients, the dosage of meropenem had been indicated in the clinical notes. The mean dosage of meropenem was 693.6±417.2 mg. Dose frequency was indicated for 282 (97.6%) of the patients. Majority of the patients, 229 (79.2%) received 8 hourly and 12 hourly (20.6%) doses. The duration of therapy was indicated in 264 (91.3%) patients and was distributed as follows: <5 days 85 (32.1%), 5-14 days 165 (62.4%) and > 14 days 1 (0.4%). The duration of meropenem therapy was missing in 25 (5.5%) patients.

4.1.2.4: Clinical outcomes of patients treated with meropenem

Patients treated with meropenem showed a cure rate of 85% and were discharged while 9.7% deteriorated and 1.8% died. Some patients (0.4%) had prolonged use of meropenem whereby meropenem was administered for more than 14 days.

4.2: Section one part III: microbial resistance patterns to meropenem

Microbial resistance patterns to meropenem were obtained from isolates of the reviewed patient records and the archived laboratory data.

4.2.1: Resistance to meropenem by patient isolates

4.2.1.1: Susceptibility testing and meropenem prescribing

In this study, meropenem was prescribed empirically to 348 (77%) of the patients. In 104 (23%) patients, meropenem was administered after culture and sensitivity reports. Out of the patients for whom culture and sensitivity test was ordered, 26 (25%) of the results were received within three days while for 78 (75%), they were received after three days.

The mean interval between prescribing and receiving a CST report was 3.22±3.2 days (range 1-15 days). From the samples taken from patients, more gram-negative bacteria 82, (97.6) were isolated. The most frequently isolated micro-organisms were *Klebsiella pneumonia,* 28 (39.4%) and *Escherichia coli,* 19 (26.8%).

The gram-negative bacteria, 24 (33.8%) were more resistant to meropenem compared to the gram-positive micro-organisms (p-value<0.001). Resistance was high amongst *Acinetobacter baumannii* (90.0%) and *Pseudomonas aeruginosa* (55.6%) isolates.
The laboratory findings on susceptibility are summarized in Table 4.7.

Table 4.7: Micro-organisms isolated from patients on meropenem at Kenyatta National Hospital

Micro-organism isolated	Susceptible, n (%)	Resistant, n (%)	Total
Klebsiella pneumoniae	25 (89.3)	3 (10.7)	28
Escherichia coli	13 (68.4)	6 (31.6)	19
Pseudomonas aeruginosa	4 (44.4)	5(55.6)	9
Acinetobacter baumannii	1 (10.0)	9 (90)	10
Neisseria meningitides	-	1 (100)	1
Streptococcus pneumoniae	2 (100)	-	2
Streptococcus pyogens	1 (100)	-	1
Proteus mirabilis	1 (100)	-	1
Total	47	24	71

4.2.1.2: Meropenem resistance patterns from archived laboratory database at KNH

The most resistant microorganism isolated was *Acinetobacter baumannii* 357 (79.5%) whereas *Escherichia coli* were the most susceptible, 921 (84.2%) as shown in Table 4.8.

Table 4.8: Resistance patterns for gram-negative bacteria against meropenem at Kenyatta National Hospital

	Resistance, n (%)	
Micro-organism	**2016**	**2017**
Klebsiella pneumoniae	289 (40)	160 (38.8)
Pseudomonas aeruginosa	192 (74.7)	185 (69.8)
Escherichia coli	64 (12.8)	109 (21.9)
Acinetobacter baumannii	208 (80.7)	149 (78.4)
Total	753	603

There was no statistical difference in resistance to meropenem among the isolated gram-negative bacteria at Kenyatta National Hospital between 2016 and 2017 (p value=0.213). *Escherichia coli* were the most susceptible with its resistance to meropenem increasing over from 12.8% in 2016 to 21.9% in 2017. The largest increase in resistance was observed with *Acinetobacter baumannii* for the same number of isolates. However, *Pseudomonas aeruginosa* resistance to meropenem decreased from 2016 to 2017 by 4.9%. There were more isolates in 2016 for all microorganisms except for Escherichia coli which was highly isolated in 2017. However, there was no significant change in the overall resistance as illustrated in Figure 4.2.

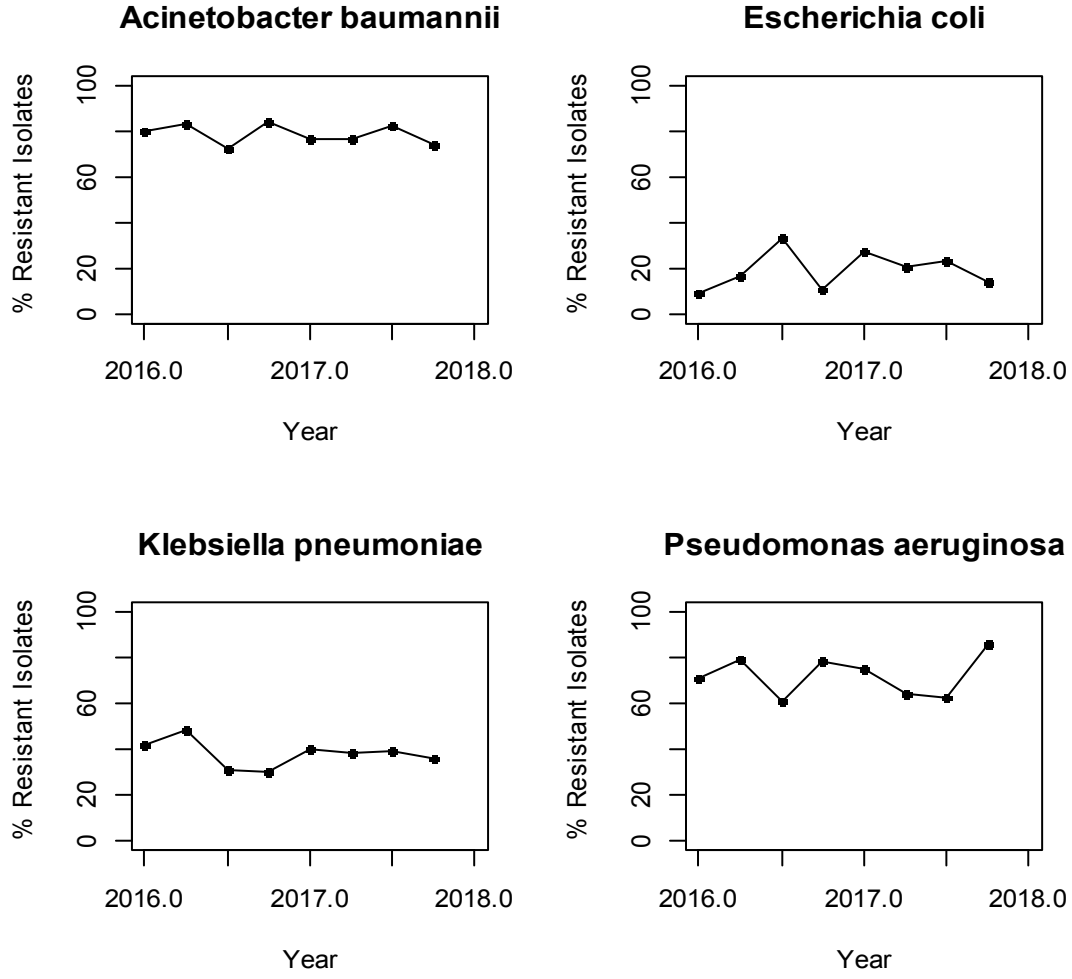

Figure 4.2: Meropenem resistance patterns at KNH in 2016 and 2017

4.3: Meropenem Consumption at KNH

There was a general downward trend in meropenem consumption over the two-year period from an average of 7047250 mg in 2016 to 5484375 mg in 2017. There is an atypical component in January to March of 2017 whereby there was a sharp decrease in meropenem consumption from 7550000mg between October and November 2016 to 2505000mg between January and March 2017. The highest consumption of meropenem was recorded April and June 2017, (7987500mg) and the least consumption was between January and March 2017, (2505000mg) as shown in Figure 4.3.

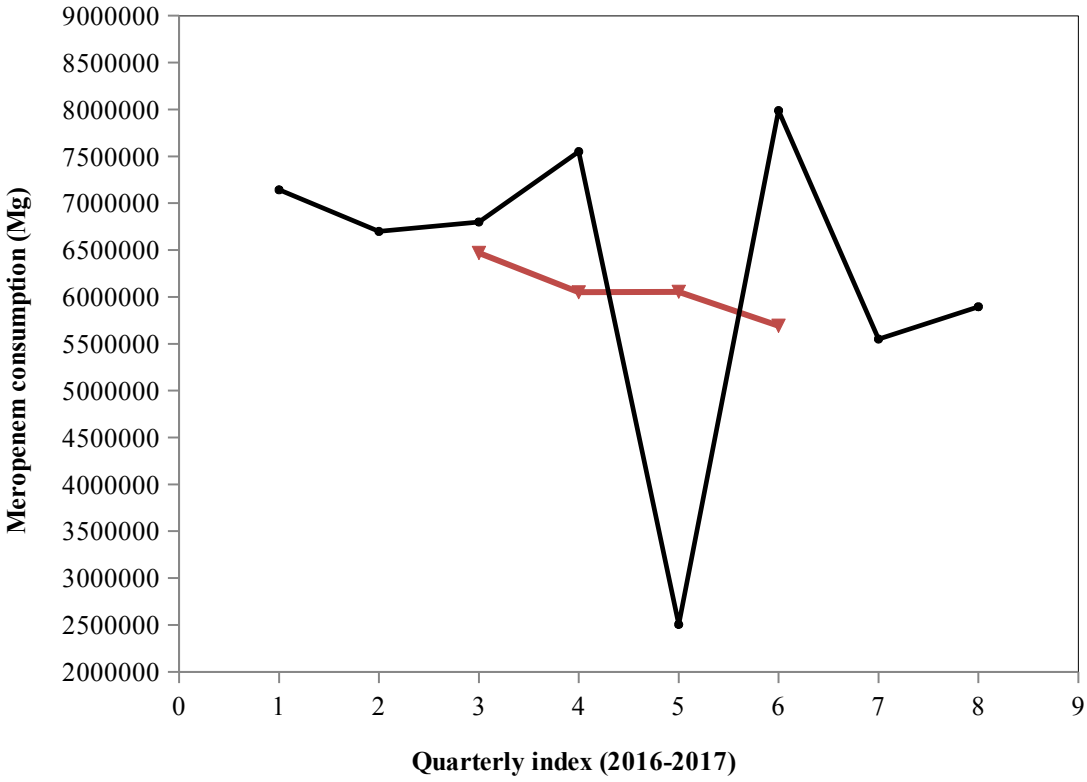

Figure 4.3: Trend of meropenem consumption between 2016 and 2017 at Kenyatta National Hospital

4.4: Section two: knowledge, attitudes and practices of clinicians on meropenem use

4.4.1: Baseline Characteristics of the Clinicians

A total of 60 clinicians were issued with questionnaires of whom 39 (65%) responded. The baseline characteristics of the clinicians who participated in the study are as shown in Table 4.10. All the clinicians practiced in both the in-patient and out-patient clinics.

Table 4.9: Characteristics of clinicians prescribing meropenem at Kenyatta National Hospital

Characteristic	n (%)
Gender	
Male	19 (48.7)
Female	20 (51.3)
Total	39
Age	
25-30	6 (15.4)
31-45	25 (64.1)
46-60	2 (0.5)
Missing	6 (15.4)
Total	39
Training	
Local	30 (76.9)
Foreign	9 (23.1)
Total	39
Specialization	
Internal medicine	11 (42.3)
General Surgery	7 (26.9)
Pediatricians	3 (11.5)
Obstetrics/gynecology	2 (7.7)
Neurosurgery	1 (3.8)
Orthopedic	1 (3.8)
Oncology	1 (3.8)
Missing	13 (33.3)
Total	39
Duration of practice	
<4 years	7 (17.9)
>4 years	32 (82.1)
Total	39

The clinicians were equally distributed in terms of gender. Their ages ranged between 29-60 years with the majority 25, (64.1%) being aged 31-45 years with a mean age of 34 years. Majority of the clinicians, 30 (73.9%) were locally trained and 31 (79.5%) had been in practice for more than four years. Internal medicine had the highest specialization with 11 (42.3%) clinicians.

4.4.2: Meropenem prescribing practices of clinicians

In this regard, 12 (30.8%) clinicians reported that they prescribe meropenem at most one to two times weekly and only 1(2.6%) prescribed once every two months as presented in Table 4.10.

Table 4.10: Meropenem prescribing practices of clinicians at Kenyatta National Hospital

Prescribing practice	n (%)
1-2 times weekly	12 (30.8)
Once a month	9 (23.1)
Occasional	5 (12.8)
Daily	4 (10.3)
Rarely	4 (10.3)
Twice a month	2 (5.1)
Every 2 months	2 (5.1)
2-3 times monthly	1 (2.6)
Total	39

Clinicians were broadly categorized into two groups based on the prescribing practice. Those who prescribed daily or one to twice weekly were categorized as high-frequency prescribers while those who prescribed once monthly or less were categorized as low-frequency prescribers. The high-frequency prescribers were 16 (41%) while the low-frequency prescribers were 23 (59%).

4.4.3: Demographic factors affecting meropenem prescribing by clinicians

There was a significant association between specialization and meropenem prescribing practices (p=0.04) as illustrated in Table 4.11. There was no statistically significant association between clinicians' gender, age, training and duration of practice and meropenem prescribing practices.

Table 4.11: Association between demographic characteristics and prescribing practices of clinicians at Kenyatta National Hospital

Characteristic	High frequency prescribers	Low frequency prescribers	p-value
Gender			
Males	8 (20.5%)	11 (28.2%)	p=0.894
Females	8 (20.5%)	12 (30.8%)	
Total	16	23	
Age			
<35 years	10 (30.3%)	15 (45.5%)	p=0.21
35 years and above	4 (12.1%)	4 (12.1%)	
Missing	6 (15.4)		
Total	14	19	
Training			
Local	12 (40%)	18 (60%)	p=0.812
Foreign	4 (44.4%)	5 (55.6%)	
Total	16	23	
Duration of practice			
<4 years	4 (57.1%)	3 (42.9%)	p=0.339
>4 years	20 (62.5%)	12 (37.5%)	
Total	24	15	
Specialization			
Neurosurgery	1 (100%)	0 (0%)	p=0.04*
Obstetrics/gynecology	1 (50%)	1 (50%)	
Oncology	0 (0%)	1 (100%)	
Orthopedics	0 (0%)	1 (100%)	
Pediatrics	3 (100%)	0 (0%)	
Plastic surgery	5 (71.4%)	2 (28.6%)	
Internal medicine	1 (9.1%)	10 (90.9%)	

4.4.4: Factors affecting meropenem prescribing practices of clinicians

Most of the clinicians relied on multiple factors while prescribing meropenem. The predominant ones were advice from an Infectious Disease Specialist 22 (56.4%) and senior colleagues 20 (51.3%). The Pharmacists, 5 (12.8%) were the least accessible to guide meropenem prescribing. These factors are shown in Table 4.12.

Table 4.12: Factors affecting meropenem prescribing practices of clinicians at Kenyatta National Hospital

Factors	Number of clinicians, n (%)
Infectious disease specialist advice	22 (56.4)
Senior colleague advice	20 (51.3)
Previous experience with meropenem	17 (43.6)
Availability of guidelines	17 (43.6)
Microbiologist advice	19 (48.7)
Pharmacist advice	5 (12.8)

4.4.5: Knowledge on the availability of meropenem prescribing guidelines and training

Majority of the clinicians 22 (56.4%) did not know about the existence of meropenem prescribing guidelines at KNH hence they tended to rely on clinical experience. However, 17 (43.6%) were aware of meropenem prescribing guidelines as contained in the KNH guide to antimicrobial therapy in critical care units (CCUs) of whom 16 (94.1%) referred to the guidelines occasionally. Only 9 (23.1%) of the sampled clinicians had received training on meropenem prescribing which was through: lectures 3 (7.7%), workshops 4 (10.3%) and self-directed learning 2 (5.1%).

4.4.6: Knowledge and attitudes of clinicians on restricted meropenem prescribing

Out of the interviewed clinicians, 13 (33.3%) knew of the existence of restrictions on meropenem prescribing while 26(66.7%) reported that there were no such restrictions. However, 30(76.9%) of all clinicians were in agreement that KNH should have restrictions

on meropenem prescribing. A total of 29 (74.4%) clinicians strongly advocated for the cessation of empirical use of meropenem at KNH and in any clinical practice. However, the rest believed that empirical use should continue due to the unavailability of prompt CST reports.

4.4.7: Knowledge and attitudes of clinicians on meropenem resistance and dose adjustment in renal failure

A total of 24 (61.5%) clinicians believed that meropenem resistance is a major problem in clinical practice while 12 (30.8%) and 9 (23.1%) stated that it is only a KNH and national problem respectively. Most of the clinicians did not have any knowledge of the levels of meropenem resistance at KNH.

Majority of the clinicians, 34 (87.2%) acknowledged that doses of meropenem should be adjusted in patients with renal failure. Most of the clinicians, 34 (87.2%) thought it was important for clinical pharmacists to review all the prescriptions containing meropenem and any other antibiotic.

4.4.8: Perceptions of causes of meropenem resistance

Three factors were perceived as the major causes of meropenem resistance. These included over-prescription and overconsumption 28 (71.8%), inappropriate choice of antibiotics 22 (56.4%) and failure to complete prescribed treatment 17 (43.6%).

4.4.9: Ordering culture and sensitivity tests by clinicians

A total of 20 (51.3%) of the clinicians stated that they only order culture and sensitivity tests (CST) when the patients do not respond to empiric therapy while 18 (46.2%) stated that it was a requirement to order for CST before the commencement of meropenem. The challenge most clinicians faced with CST was delayed results 34 (87.2%).

4.4.10: Potential interventions to improve meropenem prescribing

The three measures rated as the most helpful interventions for improving meropenem prescribing were availability of guidelines 39 (100%), educational sessions 21 (53.8%), and advice from a Clinical Microbiologist and an Infectious Diseases Specialist
15 (38.5%).

5.0: CHAPTER FIVE: DISCUSSION

This study aimed at describing meropenem use, its resistance patterns and the factors that influence clinicians to prescribe meropenem.

5.1: Patterns of meropenem use

5.1.1: Indications of meropenem

Soft tissue infection was the most common diagnosis in this study. However, this differed with the Iranian study of 2015, where meropenem was mostly prescribed for severe sepsis, meningitis and pneumonia with a frequency of 26.3%, 17.1% and 15.3% respectively. Another study conducted in 2016 at the Srinagarind Hospital, reported that meropenem was used as an empiric therapy (65.1%) and respiratory tract infections and sepsis were the most common diagnosis (43). In this study, it was realized that there were instances where meropenem was used in patients with tuberculosis. This could be explained by the fact that meropenem might have been used in such patients for other bacterial co-infection.

5.1.2: Problems with meropenem use

In this study, meropenem was majorly used empirically. In some patients, meropenem was administered for less than 5 days, duration of therapy, dosage and frequency of administration were not documented. This observation was similar to a study conducted on febrile neutropenic patients which reported that irrational and inappropriate use of meropenem in a healthcare setting is a common practice (27). In this study, there were instances where meropenem was administered as a 24-hourly dose and this was inconsistent with KNH meropenem prescribing guidelines (37). This implies that there is a need to sensitize the clinicians on the existing guidelines and the need to strictly adhere to them when prescribing meropenem.

The study found out that, meropenem was often prescribed without the support of culture and sensitivity reports. This implies that much of the meropenem was prescribed based on the clinicians' clinical decisions or experiences. These results were comparable to those of a study conducted in a French hospital in 2012, where 60% of meropenem was prescribed empirically (11). Similarly, a study conducted at Sukhothai hospital in Thailand, reported that meropenem was used empirically in 95% of the cases (12)**.** In another study conducted at a tertiary care university hospital in Northern Iran, it was reported that meropenem culture and sensitivity reports were available in only 38% of the prescriptions (7). It,

therefore, seems to be reasonable to promote utilization of culture and sensitivity tests when prescribing broad-spectrum antibiotics such as meropenem. This could be through the provision of sample collection containers in the wards, provision of culture media at the laboratories and enshrining the reliance on culture and sensitivity results in the clinicians' practice.

5.2: Meropenem resistance patterns

In this study, data from patients' and archived laboratory records showed that *Acinetobacter baumannii* had the highest resistance to meropenem while *Klebsiella pneumoniae* and *Escherichia coli* isolates had the lowest resistance. This observation was similar to reports of the study on febrile neutropenic patients which reported a similar resistance pattern to meropenem by *Klebsiella pneumoniae* and *Escherichia coli* (27).

The lack of documented microbial growth in some of the patients' samples may be interpreted in two ways. One is that the patients probably had no bacterial infection to warrant the use of meropenem. Secondly, at times, samples were drawn for culture and sensitivity testing when patients already had one or several courses of antibiotic therapy. Sometimes these antibiotics are initiated within the hospital or the patients come after they have already received them in other health facilities before referral. Previous antimicrobial therapy reduces the yield and accuracy of cultures for the isolation of microorganisms (44, 45).

In both scenarios, there is an element of inappropriate antibiotic use that promotes the development of resistance. It is therefore prudent to follow the principles of antimicrobial therapy which directs that, all efforts should be made to get a sample for CST prior/immediately after initiation of meropenem. This would help in identifying resistance patterns and hence promote the rational use of meropenem.

5.3: Clinicians' knowledge, attitude and practice with meropenem

Assessing the contextual factors that guide antibiotic use and meropenem in particular, is an important step in reducing antimicrobial resistance.

In this study, it was observed that clinicians viewed meropenem resistance as a problem in clinical practice (61.5%), at the facility level (30.8%) and nationally (23.1%). This observation was similar to the reports of a study involving junior doctors in France and Scotland (6) which reported that 95% of the clinicians perceived antibiotic resistance as a national problem and 63% perceived it as a problem in their clinical practice. These results

were similar to those of a study conducted at Concord hospital in 2009 reported that 96% of the respondents agreed that hospitals in general face antimicrobial resistance and 93% agreed that their specific hospitals faced the same problem (45). This means that antimicrobial resistance is a worldwide problem hence the need to follow the national action plans on AMR in existence.

Training did not appear to be associated with a better awareness of meropenem resistance in this study. This is because only 23.1% of the clinicians had received training on meropenem prescribing. However, one survey done on junior and senior internal medicine doctors reported that previous experience with resistance was the best predictor of better recognition of the problem of antibiotic resistance in practice (46). A higher level of awareness of antibiotic resistance has been realized in more recent studies (47). This implies that, generally, learning of AMR in training in conjunction with previous clinical experience is an important aspect in detecting the development of resistance. This would prompt clinicians to prioritize the ordering of culture and sensitivity tests

From the results of this study and those of a study on doctors in France and Scotland (6), restricted meropenem prescribing was perceived to help reduce the development of resistance. However, some clinicians in this study were against restricted meropenem prescribing since they perceived it as undervaluing their intuition and vast clinical experience. These were comparable to a study conducted in Australia (46). Some clinicians proposed a review of the existing guidelines to avoid the use of meropenem as an empirical therapy and make microbial culture and sensitivity report a mandatory requirement before prescribing meropenem. Despite the availability of other antibiotics which could be used in place of meropenem, the clinicians reported that most of them were not in continuous supply hence the reason why they had to use meropenem. This calls for the procurement of alternatives to reduce the over-reliance on meropenem and consequently lowering the chances of resistance of development.

The availability of infectious disease specialists, senior colleagues and clinical microbiologists was highly valued by the clinicians in this study. This observation was similar to the findings of a study conducted in Australia that surveyed medical staff attitudes towards an antibiotic approval and stewardship program (46). In the Australian study, 85% of the respondents believed that seeking approval made teams think carefully

about the choice of antibiotics. In that study, 33% of the clinicians felt that consulting the antimicrobial stewardship team was time-consuming and distracting from clinical duties while 10% felt that it undervalued self-insight and clinical experience. Availability of meropenem use guidelines and sensitization on their use, continuous professional training on the new trends in practice and continuous consultation with infectious disease specialists are the major interventions towards reducing the incidence of meropenem resistance at KNH and nationally.

5.6: Study Limitations

This being a retrospective study, some patient data were missing. There were some discrepancies between the pharmacy records and the actual patient treatment sheets. In this case, some patients to whom meropenem was dispensed did not reflect in the treatment sheet. Some clinicians did not fill the entire questionnaire hence some data were missing from their responses. Like with most surveys, there is a likelihood that clinicians gave socially desirable answers. The small number of clinicians who participated in the study may lower the validity of the findings and may not reflect the actual practice in general. Data on meropenem consumption was not adequately collected since it was not the mainstay of this study.

5.7: Dissemination of Results

The final thesis was delivered to the University of Nairobi repository and College of Health Sciences Library, Department of Pharmacology and Pharmacognosy. The results were also disseminated to Kenyatta National Hospital to inform of continuous medical education. The findings are to be published in a peer-reviewed journal. The findings of this study were presented in conferences, continuous medical sessions and to Kenyatta National Hospital departments from which the respondents were sought.

6.0: CHAPTER 6: CONCLUSIONS AND RECOMMENDATIONS

6.1: Conclusion

Meropenem was mainly used as an empirical therapy at KNH. Continuous medical education, functional drug and therapeutic committees and regular drug utilization research programs could help in accomplishing the milestone of rational meropenem and other antimicrobial use. The rational use of meropenem will go a long way in reducing antimicrobial resistance.

6.2: Recommendations

6.2.1: Recommendations for practice

There is a need for regulation and proper documentation of meropenem and other antibiotics issued to patients at the pharmacy. This was occasioned by the fact that dispensing records did not tally with treatment sheets in that meropenem was missing in some of the treatment sheets whilst it had been dispensed from the pharmacy. There is a need to sensitize clinicians on the availability of prescribing guidelines and enforce them. This is through continuous medical training and periodic meropenem use evaluations. Restrictions on who should prescribe meropenem should be enforced. This will go a long way in reducing meropenem resistance. Clinicians should be encouraged to make use of the existing infectious disease specialists to make careful choices of the antimicrobials to administer. Since there are very few infectious disease specialists, there is a need to train more to meet the service need at KNH and other health facilities in Kenya.

Pharmacists were the least consulted professionals during meropenem prescribing. Most clinicians stated that the pharmacists were never available during clinical ward rounds. They challenged the clinical pharmacists to take up the task since they ought to be part of the patient management team by not only availing the required medicines but also in drawing the patient management plan together with the clinicians. KNH should consider guidelines regarding meropenem use, which should include a requirement of an infectious disease consultation before the initiation of meropenem.

6.3: Recommendations for Further Research

This study highly recommends that studies be carried out to compare meropenem utilization patterns and other carbapenems. It also recommends for a broader study on the use of other restricted antibiotics. The need for similar studies in other hospitals in Kenya is recommended.

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APPENDICES

Appendix A: Eligibility Checklist

All participants must meet eligibility criteria based on the inclusion/exclusion criteria detailed in the application for approval by the KNH/UoN Research and Ethics committee**.**

Study information

Study title		
Principal investigator name		signature
Date of recruitment		

Patient information

Patient code	
Sex	Male Female

Inclusion/exclusion criteria (Tick where appropriate)

Inclusion criteria	Yes	No
Will have been admitted in the wards at KNH		
Their records would be retrievable for the period between 2016 and 2017		
Will have been treated with meropenem		
Exclusion criteria		
Have no meropenem in their prescriptions		
Will not be in-patients		

Appendix B: Data Extraction Form

Data extraction form for meropenem use in hospitalized patients at Kenyatta National Hospital.

PATIENT UNIQUE ID **Date**

D M Y YY Y

1. Patient Demographics
   i. Gender of the patient

   Male ( ) Female ( )

   ii. Age of the patient in years ( )

   iii. Height of patients in cm ( )

   iv. Weight if the patient in kilograms ( )

2. What type of infection has the patient been diagnosed with? (tick appropriately)

Meropenem prescription	
Bacterial meningitis	
Severe pneumonia	
Soft tissue infections	
Intra-abdominal infection	
Urinary tract infection	
Post- partum infection	
Febrile neutropenia.	
Other (specify)	

3. What were the indicators of meropenem?

Meropenem prescription	Dosage	Dose frequency	Duration of therapy
1			
2			

4. Is the treatment empirical or targeted?

   Empirical ( ) Targeted ( )

5. If empirical, was the therapy in compliance to the guideline?

   Yes ( ) No ( )

6. Was a sample taken for culture and susceptibility testing taken before meropenem was initiated?

   Yes ( ) No ( )

7. If yes, on which date was a CST requested? …….

   DD MM Y

8. When was the report received in the ward? ……..

   DD MM Y

9. What is the meropenem susceptibility profile for the micro-organisms isolated?

Micro-organism	**Resistant**	**Susceptible**
Streptococcus aureus		
Streptococcus pneumoniae		
Streptococcus pyogens		
Enterococcus foecalis		
Pseudomonas aeruginosa		
Escherichia coli		
Proteus mirabilis		
Haemophilus influenzae		
Neisseria meningitidis		
Peptostreptococcus species		
Klebsiella pneumoniae		
Other		

10. If CST report is available, did it inform the choice of meropenem use?

    Yes ( ) No ( )

11. Were there any side effects associated with meropenem use?

    Yes ( ) No ( )

12. If yes, describe them and how they were managed

13. What were the clinical outcomes after meropenem use?

    Patient was cured ( )

    Patient condition deteriorated ( )

    Death ( )

Appendix C: Eligibility Checklist for Clinicians

Participant information

Participant serial number		
sex	Male	Female

Inclusion/exclusion criteria (Tick appropriately)

Inclusion criteria	Yes	No
Medical consultant or post-graduate student or medical officer working at KNH		
Worked in the wards for at least 6 months		
Provided informed consent		
Exclusion criteria		
Does not meet the above criteria		

Appendix D: Statement of Consent from Prescribers

Consenting process

I am Dr. Dennis Kasyoki Makau, a postgraduate student in the school of Pharmacy at the University of Nairobi pursuing a Master's degree in Pharmacoepidemiology and Pharmacovigilance. This document is a consent form with information about the study and will be discussed with you by the investigators. Please study it carefully, seek clarification where necessary and if satisfied, I would request you to sign your name on the form. I would like you to understand that the following principles will apply to all participants in a medical research: agreement to participate is voluntary, you can leave the study at any time without necessarily giving reasons for your withdrawal and your withdrawal from the study won't have any consequences.

Introduction to the study

Increasing antibiotic resistance is one of the major concerns of health care systems throughout the world. Several factors are responsible of the emergence of this problem of which, frequent and inappropriate use of antimicrobial agents play an important role. Therefore, optimization of antibiotic use reduces development of antibiotic resistance hence lowering healthcare costs by providing cost-effective treatments. Meropenem is considered to be a potent drug for treatment of multi-drug resistant gram negative infections. However, a recent study has indicated the emergence of Meropenem resistant *Klebsiella pneumonia*e. There is an increased use of carbapenems in the hospitals, some of which may not be warranted or the prescribing patterns do not meet the national guidelines on the use of antibiotics in management of bacterial infections.

Purpose of the study

The primary objective of this study is to describe meropenem utilization patterns, its resistance and adherence to treatment guidelines. The second objective is to identify the factors that drive clinicians to prescribing meropenem.

Procedures to be followed

You will be issued with a pre-designed questionnaire that will cover your attitude and knowledge concerning meropenem prescription and resistance

Acceptance of participation in the study

I will interview you at a time of your convenience and obtain personal and medical information from you.

Risks

I do not anticipate any risks by collecting information from you. I will keep everything you tell me as confidential as possible. The results from this study may be published or presented at professional meetings but your name will not be associated with the findings.

Rights and safety as a participant

To safeguard your rights as a participant in this study, the Kenyatta National Hospital/ University of Nairobi Research and Ethics committee will review the study protocol and the informed consent process before commencing the research.

Benefits

Understanding clinicians' meropenem prescribing behaviour is fundamental when it comes to promoting its rational use and tackling the growing rates of meropenem resistance in our hospitals.

Contacts

For any further information about this study you may contact me, my academic department or the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee via the contacts below

Who to contact

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Prof. Mark Chindia-The secretary
The Kenyatta National Hospital/University of Nairobi Ethics and Research Committee
Tel. 2726300 Ext 44355, Nairobi-Kenya
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Statement of consent

I confirm that I have read or had the consent information read to me and understood the nature of the study. I understand that my participation in this study is voluntary and that I may choose to leave any time. By signing this consent form, I have not given up my legal rights as a research study participant.

Participant signature ……. Date…….

Researcher's agreement

I confirm that I have explained the nature and effect of the study to the participant named above and understood that he/she has understood and has given willingly his/her consent.

Researcher's signature…… Date……"

Appendix E: Meropenem Prescribing Questionnaire

Date of interview ---------- Serial number ----------

Part 1: Demographic data of doctors

Gender

Male ( ) Female ( )

Age in years ( )

Graduation

Local university ( ) Foreign university ( )

Specialization if any ……

Duration of practice

<4 years ( ) b) >=4 years ( )

Place of practice

Inpatient department ( )

Both outpatient and In-patient departments ( )

Part 2: Meropenem prescribing

i) How often do you prescribe meropenem?

a) Daily ( )
b) 1-2 times weekly ( )
c) 3-5 times weekly ( )
d) Other (please specify) ……

ii) What are the factors that influence you to prescribe meropenem?

a) Previous experience …….
b) Availability of guidelines ……
c) ID specialist advice …….
d) Senior colleague advice ……
e) Microbiologist advice …….
f) Pharmacist advice……
g) Patient pressure……
h) Influence from medical representatives……
i) Any other (please specify) …….

iii) I have access to an infectious disease specialist to guide prescribing

Yes ( ) No ( )

iv) Have you received any training on meropenem prescribing in the last 12 months?

Yes ( ) No ( )

v) If yes, by what means?

a) Lectures ……...

b) Workshops ……...

c) Informal education in the clinical workplace …….

d) Web-based learning ……...

e) Self-directed learning ……

vi) My facility has guidelines on meropenem prescribing

Agree ( )

Disagree ( )

vii) If you agree, when did you refer to the guidelines lastly? ……

viii) My facility has restrictions on who can prescribe high cost antibiotics like meropenem

Agree ( )

Disagree ( )

iv) The facility should have restrictions on types of antibiotics prescribed

Agree ( )

Disagree ( )

v) Doses of meropenem should be adjusted in renal failure

Agree ( )

Disagree ( )

vi) A clinical pharmacist should review all prescriptions containing antibiotics

Agree ( )

Disagree ( )

vii) Empiric meropenem therapy should be discouraged

Agree ( )

Disagree ( )

Part 3: Meropenem resistance

i) What is your perception of the problem of meropenem resistance? (tick appropriately)

a) National problem …….

b) Problem in the hospital …….

c) Problem in clinical practice ……

ii) Levels of meropenem resistance are high (indicate whether you agree or disagree)

a) Strongly agree ……

b) b) Agree ……

c) c) Neutral ……

d) d) Disagree…

d) Strongly disagree…...

iii) What are the factors contributing to meropenem resistance?

a) Treatment not completed ……

b) Inappropriate choice of antibiotics …….

c) Inadequate dosage ……...

d) Over prescription and overconsumption ……

e) Other ……...

iv) Do you routinely order for culture and sensitivity tests? Tick appropriately

a) Always…….

b) Sometimes……...

c) Not certain……...

d) Rarely……

e) Never……...

v) What are the reasons for requesting for CST?

a) It is a requirement ( )

b) If patient does not respond to empirical therapy ( )

vi) What challenges do you have with CST?

a) Delayed results ( )

b) Difficulty in interpreting the results ( )

c) Laboratory unable to conduct such tests ( )

vii) What interventions can you suggest to improve rational meropenem prescribing?

a) …….

b) …….

c) …….

d) …….

e) …….

Appendix F: Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (Knh/Uon-Erc)

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Ref: KNH-ERC/A/277

July 11 2018

Dennis Kasyoki Makau
Reg. No.U51/87686/17
Dept.of Pharmacology and Pharmacognosy
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Dennis

RESEARCH PROPOSAL – MEROPENEM UTILIZATION, ANTIBACTERIAL RESISTANCE AND ADHERENCE TO PRESCRIBING GUIDELINES IN TWO TERTIARY HOSPITALS IN KENYA (P346/05/2018)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and approved your above research proposal. The approval period is from 11th July 2018 – 10th July 2019.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH-UoN ERC before implementation.
c) Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e) Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
f) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
g) Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

For more details consult the KNH- UoN ERC website **http://www.erc.uonbi.ac.ke**

Yours sincerely,

PROF. M. L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Director, CS, KNH
The Chairperson, KNH-UON ERC
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