MEDICATION RELATED PROBLEMS AMONG PATIENTS ON ANTIBIOTIC THERAPY IN THE MEDICAL WARDS AT KENYATTA NATIONAL HOSPITAL

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DECEMBER, 2019

DECLARATION

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APPROVAL BY SUPERVISORS

This is to acknowledge that this dissertation has been submitted for review with our approval as the University supervisors:

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DEDICATION

To God for His endless love and care. May the work of my hands be always under His guidance, and be a blessing to others.

To my family, for their constant love and support: My parents Joel and Grace; My wife Caroline; My son Ivan; My sisters; Hellen, Jackline, Nelly, Mercy and Viola and Brothers; Nelson, Hillary and Oscar.

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ABBREVIATIONS AND ACRONYMS

MRPs Medication related problems

DRPs Drug related problems

DDI Drug-drug interaction

FRD Failure to receive drug

OD Over dosage

IDS Improper drug selection

IWD/UI Indication without drug/Untreated indication

DWI Drug without indication

STD Sub therapeutic dosage

ADR Adverse drug reaction

KNH Kenyatta National Hospital.

AKI Acute kidney injury

CKD Chronic kidney disease

USA United States of America

CDI *Clostridium difficile* infection

UTI Urinary tract infection.

HIV Human immunodeficiency virus

KNH/UoN ERC Kenyatta National Hospital/University of Nairobi Ethics and Research Committee.

OPERATIONAL DEFINITION OF TERMS

Antibiotics: Natural substances produced by fungi, bacteria or actinomycetes, or synthetic derivatives thereof, that kill or suppress the growth of bacteria

Medication related problems: Are patient drug use outcomes that occur either through inappropriate prescribing, drug unavailability, dispensing error, noncompliance by the patient, idiosyncratic response by the patient to the prescribed drug or from lack of or inadequate drug use monitoring that interferes or potentially interferes with the achievement of maximal benefit of medical therapy by the patient

Prophylaxis: As regards antibiotics, is the use of an antibiotic to prevent the occurrence of a disease e.g. use of cotrimoxazole to prevent Jiroveci pneumonia in HIV infection.

Prevalence: Is the measure of the proportion of cases (e.g. MRPs) in a specified population at a specific point in time.

Pharmaceutical care: Is responsible medical therapy provision to achieve clear outcomes that improve patients' lives.

Antibacterial resistance: A change by a bacteria e.g. genetically, leading to a reduction or absolute ineffectiveness of previously effective antibiotics against the same bacteria.

Adherence: Is defined as the extent to which patients take medications as prescribed by their health care providers.

Severe MRPs: Are MRPs that can cause potential harm to the patient if left unaddressed, for example severe hypokalemia or hyperkalemia.

Moderate MRPs: Are less severe MRPs but can progress to serious and severe MRPs if left unaddressed and thus need monitoring, for example the need for monitoring of international normalized ratio (INR) in the use of antibiotics, and other drugs, with warfarin.

Mild MRPs: Are MRPs unforeseen to result in potential harm to the patient and doesn't necessarily necessitate therapeutic intervention or change of treatment.

ABSTRACT

Background: Medication related problems (MRPs), are patient drug use outcomes that affect the achievement of optimal benefit of drug therapy. Errors in drug prescribing, administration, monitoring or dispensing, antibiotic unavailability, non-adherence by the patient and idiosyncratic response to antibiotic use all contribute to MRP occurrence.

Objectives: This study aimed to investigate the prevalence of MRPs among patients on antibiotics in the medical wards at Kenyatta National Hospital (KNH).

Methodology: Cross sectional study design was adopted for this study. Ninety four participants were systematically selected from patients admitted in the medical wards. The prevalence of the MRPs as classified by Hepler and Strand (1990) were then determined through participant interview and medication record review. Continuous normally distributed variables were presented as means and standard deviations, while median and interquartile range were used to describe continuous non-normally distributed variables. Categorical variables, at 95% level of significance, were presented as frequencies and percent proportions Stata 13 software was used to infer association between the MRPs and variables. Chi-Square, Fischer's exact test, Wilcoxon rank sum test, Shapiro and Wilks test for normality were used, where appropriate, to derive the inferences.

Results: Drug-drug interactions (13.8%), improper drug selection (13.8%) and over dosage (12.8%) were the most prevalent MRPs due to antibiotic use. The bivariate analysis to assess the factors associated with the MRPs found out that marital status (**p=0.025**), lower estimated glomerular filtration rate, eGFR, (**p=0.016**), ceftriaxone (**p=0.015**), carbapenems (**p=0.033**) and ceftazidime use (**p=0.001**) were significantly associated with the occurrence of MRPs. On multivariate logistic regression analysis of these variables to assess their joint effect, the only variables which explained the prevalence of the MRPs were the use of ceftazidime (**OR: 5.62 (95% CI: 1.34, 23.5)** and lower eGFR (**OR: 5.22 (95% CI: 1.18, 23.0).**

Conclusion: MRPs regarding use of antibiotics are prevalent despite their preventability. To forestall the rising bacterial resistance, control unnecessary healthcare burden and decrease morbidity and mortality due to antibiotic use, there is a need for concerted effort from medical institutions and health care personnel to promote rational antibiotic use and prevent MRPs that hamper achievement of quality health outcomes for the patients.

CHAPTER ONE: INTRODUCTION

1.1. Background.

Medication related problems (MRPs), also known as drug related problems (DRPs), are patient drug use outcomes that occur either through inappropriate prescribing, drug unavailability, dispensing error, noncompliance by the patient, idiosyncratic response by the patient to the prescribed drug or from lack of or inadequate drug use monitoring that interferes or potentially interferes with the achievement of maximal benefit of medical therapy by the patient(1). Identification of real and likely DRPs, correction of the actual DRPs and prevention of the likely DRPs is the core function of pharmaceutical care, which according to Hepler and Strand, is defined as responsible medical therapy provision to achieve clear outcomes that improve patients' lives(1). According to Hepler and Strand 1990,there are eight subclasses of MRPs and comprise; Adverse drug reaction(ADR), Untreated indication/ Indication without drug(UI/IWD), Drug interactions (DI) Sub-therapeutic dosage(STD), Failure to receive drug(FRD), Drug without indication(DWI), Improper drug selection(IDS), and Over dosage (OD).

Antibiotics are natural substances produced by fungi, bacteria or actinomycetes, or their synthetic derivatives, that kill or suppress the growth of bacteria. They differ in their physical, chemical, pharmacological properties and in their antimicrobial spectra. They are classified based on these differences with those that have the same chemical structure, and or pharmacological properties being classified in the same group(2).

MRPs among patients on antibiotics can have significant consequences of neurological complications(3), longer hospital stays, increased treatment and drug associated morbidity and mortality(4). Antibiotic overuse (over-prescription)(5), inappropriate prescribing (incorrect treatment duration, indication or agent choice,) in bacterial infections, widespread agricultural use, few available antibiotics and regulatory hurdles in clinical trials of new antibiotics contributes to the proliferation of multi-drug resistant bacteria (6). Bacterial resistance is a current serious threat with the use of antibiotics, and an important health care concern both locally(7)(8), regionally(9) and globally(10).

1.2. Problem statement.

Inappropriate, and/or appropriate, antibiotic use is associated with the potential of adverse drug reactions which can result in increased hospital stay, increased health care costs(11)(12) and or mortality(13). The development of resistance by bacteria to most of the commonly used antibacterial agents complicates the management of antibiotic resistant bacterial infections leading to increased hospital stay, costs, and morbidity and mortality(14).In a study in 2013 on rational use of medicines at KNH, it was found out that 96.5% of the prescriptions were irrational, medication error prevalence was 45% and 71.2% of the medication errors concerned inappropriate duration(15).

Another study done at KNH in 2017 on prevalence of antibiotic use indicated a 22.2% prevalence of antibiotic use in the medical wards and the most widely prescribed antibiotic class, cephalosporins, at 37.2% , recorded bacterial resistance as high as 90%. *Pseudomonas aeruginosa* bacteria recorded high resistance to meropenem at 57% and to amikacin at 46% (16). Another study done in 2015-2016 in the medical wards at KNH, on bacterial antimicrobial susceptibility patterns, identified multi drug resistance as high as 88% (retrospective arm). Resistance to ceftriaxone was found to be 82% in the prospective arm and it was noted that 51% of the patients received cephalosporins for empirical treatment(8). Another study at KNH investigating the extent of MRPs in medical patients identified 338 MRPs of which 84% were due to drug interactions, over dosage, non-treated indications and adverse drug reactions, and importantly, 91% of them were considered preventable(17).

Unnecessary use of antimicrobials in noninfectious/nonbacterial syndromes or for longer duration than needed fuels the proliferation of antimicrobial resistant nosocomial microbes, a local and global concern in the management of most bacterial infections(14)(18).

Antibiotics play a critical role in the management of bacterial infections that untreated infections or even a delay in the administration of antibiotics in severe bacterial infections is associated with increased mortality(19)(20).

Even though previous studies done at the hospital have highlighted the concern of irrational drug use, medication errors, inappropriate dosing, drug interactions, and

adverse drug reactions, none of the studies has exclusively dwelt on investigation of drug related problems among patients prescribed antibiotics in the medical wards even in the context of previous reports of irrational drug use(15) and high bacterial resistance(8)(16), important local and global concerns in antibiotic use.

1.3. Study Justification.

Study on MRPs among patients particularly on antibiotics in this set up has not been done even though previous studies have highlighted the high prevalence of resistance to commonly used antibiotics (8)(16). In other studies, it has also been noted that patients in the medical wards have a high potential for MRPs because of age, concomitant conditions, or large number of drugs prescribed to these patients(21)(22)

In many studies, MRPs have been noted to be preventable. In a study in four South African hospitals, ADR-related deaths comprised 16% of admitted medical patients and 43% of the ADRs could have been prevented(13). A study by Nicholas Moore et al.(1998), also noted that ADRs contributed to 3% of hospital admissions and 77% the ADR cases were related to the pharmacology of the drug(s) and possibly preventable(12). The surge in bacterial resistance due to inappropriate prescribing is largely attributed to incorrect choice of agent or dose of antibiotic therapy. Wrongly prescribed antibiotics diminishes therapeutic outcomes and puts patients at risk of complications due to the incorrectly prescribed antibiotic therapy(6)

Notwithstanding the above problems with inappropriate antibiotic use, appropriate empiric therapy use improves survival and shortens hospital stay duration in medical patients admitted due to bacterial infections(23). Physician adherence to prescribing recommendations and clinical pharmacist's interventions through pharmaceutical care helps to identify and prevent the occurrence of DRPs(1)(24)

Antimicrobial use and infection control policies helps to decrease the incidence of infections with multidrug resistant bacteria(25), forestalls the development of resistance, reduce the incidence of adverse drug events, prevent bacterial super infections and ultimately leads to decline in health care costs(26).

Determination of MRP prevalence among patients on antibiotic therapy in the internal

medicine wards and risk factors associated with the MRPs, through this study, will help in the identification of antibiotic use problems and help complement the formulation of antibiotic use policies to prevent or minimize their occurrence.

This study also coincided with the launch of empiric antibiotic therapy guide in the hospital in February, 2018 and provides a good glimpse of antibiotic use in the medical wards, and will inform on important reviews and interventions in antibiotic use.

1.4. Study purpose.

This study investigated the prevalence of MRPs among patients on antibiotics and consequently helped to scope the extent of MRPs associated with antibiotic use and will lead to formulation of strategies to address them.

Characterization of the prevalence of the various MRPs among patients on antibiotics will provide an important guide on areas to focus in addressing rational use of antibiotics. The studies by Okiko,2017, and Wanga,2017, reflects worrying concerns as regards antibiotic resistance in the medical wards of KNH and this needs urgent address(16)(8). Findings from the study done by Huldah at KNH in 2013, on the rationality of medicine use (all drugs including antibiotics), also pointed out an important concern with the use of drugs, antibiotics not an exception, in the hospital and need for address(15).

Application of the study findings to improve rational antibiotic use through antibiotic use policies and stewardship programs will ultimately result in better patient clinical outcomes, decreased rate of development of resistance, decreased health care burden and costs, and decreased morbidity and mortality as highlighted by several studies(14) (25).

1.5. Research questions.

Research questions for the study were;

1. What is the overall MRP prevalence among patients on antibiotic therapy in the adult internal medicine wards at KNH?
2. What is the prevalence of the various types of MRPs among patients on antibiotic therapy in the adult internal medicine wards at KNH?
3. What patient associated risk factors are correlated with the various classes of MRPs among patients on antibiotic therapy in the adult internal medicine wards at KNH?

1.6. General objective.

To identify and describe the MRPs associated with antibiotic use among the medical patients at KNH.

1.6.1. Specific objectives.

1. To determine the overall MRP prevalence among patients on antibiotic therapy in the adult internal medicine wards at KNH.
2. To determine the prevalence of the various types of MRPs among patients on antibiotic therapy in the adult internal medicine wards at KNH.
3. To investigate the patient associated risk factors correlated with the various types of MRPs among patients on antibiotic therapy in the adult internal medicine wards at KNH.

1.7. Study delimitation.

This study only involved patients on antibiotics in the medical wards at KNH. This comprised medical patients admitted in wings A, B, C, D of wards 7 and 8.

1.8. Study limitations.

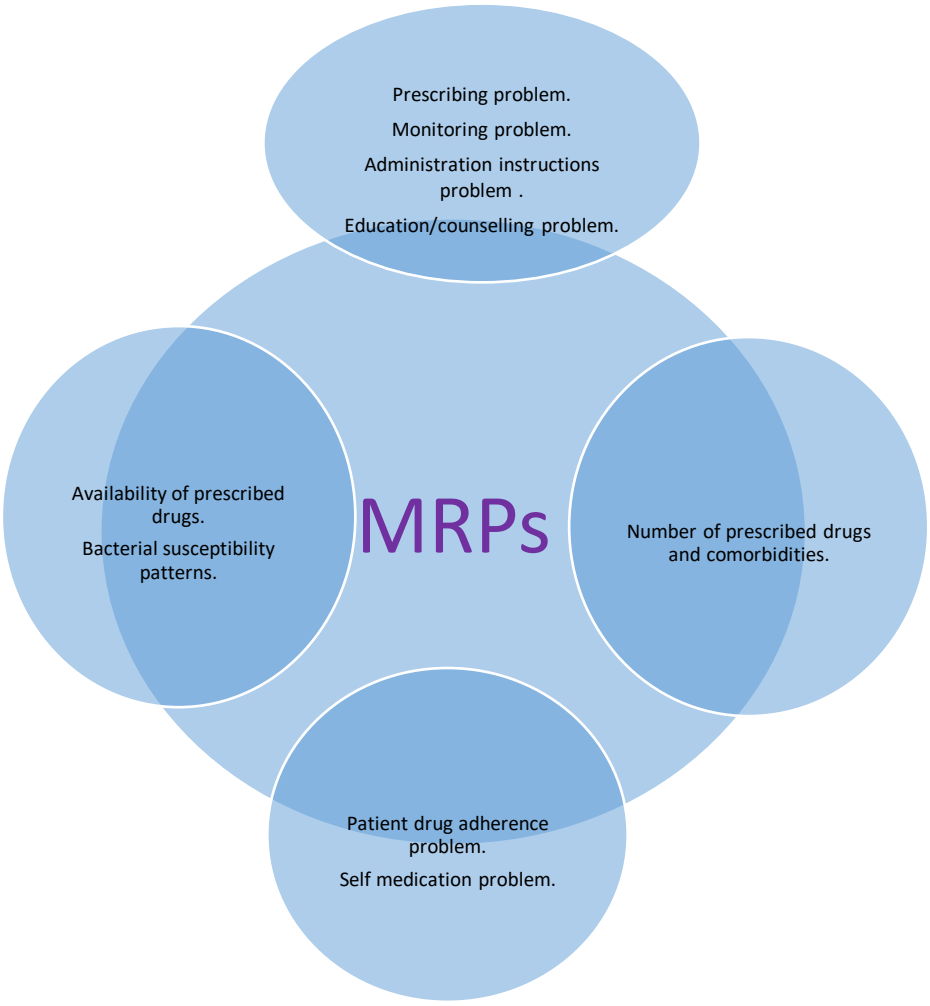
The study was carried out based on the assumption that;

1. There was no or minimal incomplete data from recruited unresponsive study patients.
2. The clinical feature(s) of concomitant disease(s), which is/are similar to the expected adverse drug event(s) of the administered antibiotic, did not mask the identification of the adverse drug event(s).
3. All prescribers in the adult medical wards had been sensitized on the KNH guide to empiric antimicrobial therapy, second edition 2018.
4. That recruited study participants were representative of the critically ill and less critical ill patients to avoid biased deductions.

1.9. Conceptual framework.

The conceptual framework depicted in figure 1 below describes the interrelationship between the various factors which contribute to MRPs in patients. The various classes of MRPs as proposed by Hepler and Strand(1) include; Adverse drug reactions (ADRs), Drug interactions (DI), Improper drug selection (IDS), Sub therapeutic dosage (STD),

Over dosage (OD), Failure to receive drug (FRD), Drug without indication (DWI), and indication without drug (IWD).



The conceptual framework is partly adapted from a study by Nyakiba et al.,2015, (17)

Figure 1.1: Conceptual framework.

KEY: MRPs-medication related problems

CHAPTER TWO: LITERATURE REVIEW

2.1. Introduction

This chapter focuses on literature review on the use of antibiotics and on the prevalence of the various classes of MRPs, as per Hepler and Strand classification (1),and the patient related factors correlated with the MRPs in medical patients prescribed, or who should be prescribed antibiotics.

2.2. Antibiotics

Antibiotics are substances obtainable from fungi, bacteria or actinomycetes that kill (bactericidal) or interfere with the growth or replication of bacteria without killing it (bacteriostatic). Antibiotics are classified into several classes based on their chemical or pharmacological properties(2).

Bacterial infections accounts for high burden of diseases worldwide contributing to disabling complications as a consequence of their infective sequel(27), and/or antibiotic use(3), increased health care costs with the use of antibiotics in their management and morbidity and mortality(28)(29).

Several bacterial species which gain entry into the bloodstream through the respiratory system, gastrointestinal system, and the skin, through breach of the skin's protective function, either through pricks, animal or human bites, intravenous access sites, non-sterile intravenous solutions or during surgical incisions, are responsible for several diseases with mild or fatal outcomes on the health of the infected individual or persons who come in contact with the infected individual for infectious diseases. Bacteria infect all body tissues and organs and are generally classified per the body organs or systems they infect i.e. respiratory tract, gastrointestinal, central nervous system, genitourinary tract, cardiovascular system and skin infections. Antibiotics are critical for the management of these bacterial diseases(30).

This important feature of antibiotics is to kill or suppress the growth of bacteria. This renders their critical role in the cure and prophylaxis of bacterial infections in medical patients. Their overuse and misuse has resulted in widespread resistance by most bacterial organisms (9)(31), with resultant increased health care costs, morbidity and mortality(14).

Resistance to bacteria is deemed to have occurred when the experimental (*in vitro*) inhibitory or bactericidal concentration far exceeds the safe dose for use in human beings (*in vivo*) . This can occur when either ineffective drug concentration reaches the target, or by inactivation or alteration of the drug and or through failure to activate the drug if pro drug used. Outward pumping of the drug (efflux) leads to inadequate intracellular drug concentration and resultant resistance. Efflux pump mechanisms is responsible for bacterial resistance to tetracyclines, macrolides, chloramphenicol, beta-lactams and fluoroquinolones. Drug inactivation is responsible for resistance to beta-lactam antibiotics and aminoglycosides by some bacteria, and failure by the bacterial cell to activate the pro-drug is responsible for resistance to Isoniazid by *M. tuberculosis*. Alteration of drug target/receptor also noted for resistance to fluoroquinolones, tetracyclines and macrolides(2).

2.3. Prevalence and risk factors correlated with MRPs in patients taking antibiotics in the medical wards at KNH.

A study done in Beirut University hospital, among hospitalized patients, identified 90 patients with DRPs. Drug interactions (37%), over dosage (28%), improper drug selection (23%), sub therapeutic dosage (10%) and improper drug administration (2%) were the most common DRPs(24).

Studies done locally on MRPs have not focused on MRPs in patients taking antibiotics despite the high rates of resistance observed in previous studies(7)(8)(16). A study on MRPs in patients with stage 3 and 4 kidney disease at KNH found that indication without drug, drug interaction, and failure to receive drug were the most commonly encountered MRPs(32). In another study MRPs comprised 10.8% and the most common were improper drug selection (26%), over dosage (22%) and sub therapeutic dosage (22%). Of the MRPs noted, 21.6% of the drugs involved were antibiotics(33).

A study in the Netherlands identified cognition impairment, four or greater comorbidities, renal function impairment, nonadherence to drug therapy regimen and polypharmacy as important risk factors for preventable MRPs(34).And in another study to assess adverse drug events risk factors in a nursing home, multiple comorbidities, use of multiple medications and use of anti-infectives posed a risk for these MRP(35).And although the

use of multiple medications is noted as a risk factor for MRPs, assignment of a strict cut-off for number of medications versus the preponderance of MRPs is not definite(36).

2.3.1. Adverse drug reactions

An adverse drug reaction is any undesired drug effect beyond its anticipated therapeutic/pharmacologic effect occurring at the usual recommended dose in clinical use for the specified medical indication(37). They are diagnosed clinically based on the temporal relationship between drug treatment initiation and the onset and end of the reaction. They are commonly dose-dependent, linked to the pharmacokinetics of the drug and resolve when the drug is stopped or dose reduced. They can either be type A(pharmacological), which is due to an augmentation of the pharmacological effects of the drug, or type B(bizarre),which implies the effect is not foreseeable from the well-known pharmacology of the drug(37).

Adverse drug reactions are responsible for about 5% of hospital admissions, 10% of hospital inpatient cases and deaths in 0.1% of medical inpatients(37). Adverse drug reactions account for increased length of hospitalization due to mimic of disease resulting in delayed diagnosis and deferred treatment, and increased health care costs due to the need for more rigorous treatment and monitoring(11)(12). Factors that makes one susceptible to adverse drug reactions include individual genetic variations in patients resulting in different pharmacokinetic and pharmacodynamic handling of drugs(38), immunological response variations, patient age, comorbid disease burden, multiple drug use(22), and drug-drug interactions(39).

The most common documented adverse drug reactions due to antibiotics include; allergic or anaphylactic reactions due to penicillins, occurring in ~10% of patients, of which about 5% of these patients will react to cephalosporins, due to the common beta- lactam ring between the two classes of drugs(40).

Neurotoxicity, nephrotoxicity, ototoxicity, peripheral neuropathy, allergic skin reactions, encephalopathy or neuromuscular blockade have also been reported due to aminoglycosides, beta lactams, tetracyclines, cotrimoxazole, macrolides, quinolones, linezolid, dalfopristin-quinupristin or polymyxins(3).

In a six-year retrospective study done in Catanzaro, Italy, between January 1995 and December 2000, ADRs associated with antibiotic therapy were found to comprise 44.9% out of the 205 identified episodes of ADRs and that withdrawal of the suspected offending drug led to recovery in 95% of the cases. This demonstrates that antibiotics are a usual cause of ADRs in hospitalized patients and thus the need for active surveillance for potential ADRs(41).

A study done in Uganda to determine the admission prevalence and hospitalization incidence of antibiotic associated adverse drug reactions (aa-ADRs) found that 19% of patients encountered at least one aa-ADR of which 16% were hospital acquired(incident cases) and mainly involved ceftriaxone, an antibiotic commonly used in our setup(42). In another study in a South African hospital serving a community with a high prevalence of HIV, 6.3% of medical inpatients developed ADRs, and drugs for opportunistic infections and antibiotics were implicated in more than 60% of the cases(22).

Another study at four South African hospitals, looking at mortality from ADRs in medical inpatients, found out that 16% of deaths were ADR-related, and HIV infection and being on ART, polypharmacy (>7 drugs used), and increased comorbidity score were factors independently associated with the ADRs. Tenofovir, rifampicin and cotrimoxazole were the most implicated drugs and 43% of the ADRs could have been prevented(13). And in a meta-analysis study, 1.6% of inpatients suffered adverse drug reactions of which 45% were preventable(43)

2.3.2 Drug-drug interactions

Drugs interaction occurs when drugs, food or herbal supplements interact resulting in a medical condition to the patient(1). This is clinically significant if one drug causes cytochrome P-450 metabolic pathway inhibition or induction and consequently affecting the metabolism of the other drug leading to untoward pharmacological effects of the drug depending on its therapeutic index or extent of concentration change of the active component of the drug on its pharmacological site of action(44).

In a study on drug toxicity to elderly patients due to drug interactions, elderly patients admitted because of hypoglycemia had been treated with cotrimoxazole and those admitted due to digoxin toxicity had been treated with clarithromycin in the preceding

weeks(45).

Warfarin interaction with most antimicrobial agents leads to interference of International Normalized Ratio posing a risk of excessive anticoagulation in patients with bacterial infections prescribed antibiotics and concomitantly using warfarin(46), erythromycin (macrolide antibiotics) with theophylline, carbamazepine, warfarin, digoxin and methylprednisolone has also been noted(47).

Drug-drug interactions, DDI can involve chelation at the gastrointestinal tract and interference with absorption or complex interactions involving the enzyme metabolic system, the cytochrome p-450, resulting in impaired metabolism of either drug and resultant toxicity and, or impaired therapeutic outcome(48). These interactions can affect all sets of patient ages but the elderly are more prone due to their age related physiologic changes, increased risk of concomitant diseases with their aging and the consequent increase in the number of prescribed medications (45).

Although drug-drug interactions are a significant cause of ADRs, increased health care costs and morbidity and mortality, drug-drug interactions are avoidable as they are predictable from clinical reports, clinical studies and insight of the pharmacologic principles regarding the drugs' use(45).

2.3.3 Improper drug selection

Improper drug selection (IDS) occurs when the patient receives an inappropriate medication for the established clinical condition. Regarding use of antibiotics, this can be improper antibiotic selection based on the patients' or local bacterial susceptibility patterns and institutional antibiotic policy/guidelines, contraindications and past medical reports of suspected or confirmed allergy for the patient. Improper drug selection can also occur if the patient's concomitant diseases and conditions are not fully considered before initiation of therapy with the drug(1).

Appropriate antibiotic selection and use is especially critical as inappropriate antibiotic use will lead to increased incidence of bacterial resistance and poor clinical outcomes(49), increased hospital costs, and increased morbidity and mortality (14).

In a study to evaluate the pattern of susceptibility of microbes that commonly cause

urinary tract infection to commonly used antimicrobial agents in Benin city, Nigeria, all the isolates showed a significantly higher resistance to tetracycline, cotrimoxazole, amoxicillin and cefuroxime, but were either moderately or highly sensitive to fluoroquinolones and nitrofurantoin, further highlighting the worrying bacterial resistance and need for the development of antimicrobial use policies and surveillance for resistant microbes(50).

And in a survey ,in a Switzerland tertiary care hospital, of inappropriate antimicrobial use patterns in the medical sections, 37.0% therapeutic and 16.6% prophylactic antibiotic prescriptions were established to be inappropriate, and 7.6% of these inappropriate prescriptions concerned incorrect choice of antimicrobials(51).

In another study evaluating the rationality of antibiotic use in a university hospital in Manisa, Turkey, out of the 16.6% of patients receiving antibiotics, 23.9% for prophylaxis, 71.4% for empiric therapy and 4.7% based on therapeutic culture results, the rational antibiotic use rate was 45.7%. Rational antibiotic use was statistically significant in patients with specimen culture results than in patients receiving antibiotics prophylactically or empirically, highlighting the significance of culture results in clinical decisions on antibiotic use. Rational antibiotic use was found to be 55.1% in the medical wards(52).

In another study evaluating inappropriate antibiotic choice and treatment effect on mortality and hospital stay duration of patients with bacterial infections, it was found out that the mortality rate was 20.1% in 36% of the 920 patients who had microbiologically determined infections and received inappropriate initial antibiotic treatment compared to 11.8% mortality rate for patients who received appropriate initial antibiotic treatment. The mean hospital stay duration was longer by at least 2 days for the group which received inappropriate empiric antibiotic treatment, compared to patients who received appropriate empiric antibiotic treatment. Even with adjustment for the medical facility and other variables, the relationship between inappropriate antibiotic therapy and mortality was significant(23), further highlighting the impact of inappropriate antibiotic selection on patient clinical outcomes.

A guide to the appropriate and accurate use of antibiotics by the Council for Appropriate

and Rational Antibiotic Therapy, USA, christened CARAT criteria, highlights the overuse and misuse of antibiotics-unwarranted use, incorrect and sub optimal antibiotic use as factors that fuels increasing antibiotic resistance. The criteria emphasizes evidence based results, therapeutic benefits, safety, optimal drug for the optimal duration and cost effectiveness as important considerations in an antibiotic selection, to ensure clinical and microbiological cure, optimal patient adherence and minimal generation of antibiotic resistance. Adoption of the criteria will lead to optimization of safe and well tolerated treatment regimens, curb unnecessary prescribing of antibiotics, decrease treatment costs, and increase adherence(53).

In another survey in Northern Ireland, United Kingdom, on point prevalence of antibiotic prescriptions, it was found out that 70% of the antibiotic prescriptions complied with the hospital antibiotic policy(54). And in a review by Marlies H., et.al on antibiotic prescribing in hospitals, it highlighted the factors that influence hospital antibiotic use and proposed improvement strategies to promote appropriate use. The review noted the need to improve antibiotic use appropriateness in hospitals through antibiotic stewardship programs for the containment of resistance(55).

2.3.4. Sub therapeutic dosage

Sub therapeutic dosage is regarded to have occurred when the patient receives too little of the drug for the medical condition(1). Sub therapeutic dosage can occur if patient factors (altered fluid status and serum albumin concentrations, weight, etc.), concomitant diseases (renal and hepatic dysfunction), and bacterial antibiotic susceptibility results are not put into consideration in antibiotic dosing decisions(56). To optimize antibiotic use outcomes, antibiotic doses have to be individualized putting into consideration the pharmacokinetic and pharmacodynamic alterations for every individual patient(57)(58).

Achievement of therapeutic antibiotic blood concentrations is critical in the use of antibiotics in the management of severe sepsis or septic shock. In a study to determine whether the serum concentration after the first dose of β-lactam antibiotics meropenem, ceftazidime, piperacillin-tazobactam and cefepime were clinically adequate to cover the less susceptible bacteria, based on minimum inhibitory concentration guidelines developed by European Committee on antimicrobial susceptibility testing (EUCAST), it

was found out that only 75%, 44%, 28% and 16% of patients who were prescribed meropenem, piperacillin-tazobactam, ceftazidime and cefepime, respectively, met the target MIC with the first antibiotic dose, implying the need for higher individualized dosing in these group of patients as opposed to the regular standard doses(59).

Sub therapeutic dosing of antibiotics is associated with the emergence of resistant bacteria. Infections with these multi drug resistant bacteria leads to poor therapeutic outcomes of antibiotic treatment and often results in high morbidity and mortality rates. To maximize antibiotic exposure, improve treatment clinical outcomes and minimize the selection of resistant bacteria, therapeutic drug monitoring of antibiotics has been noted as beneficial(60).

In severely ill patients with AKI, mortality is high, ranging from 10%-60%. There is decreased mortality rates in developed countries, ~10% in the USA, and higher in developing countries. This is partly due to the selection of antibiotic therapy inappropriate for patients with sepsis. The primary reason for the inappropriate antibiotic therapy is bacterial resistance and lack of efficacious therapy but more so the use of antibiotic doses that are sub therapeutic to achieve sufficient antibiotic concentrations at the foci of the bacterial infection. This further points to the necessity of higher therapeutic, non- conventional doses, in the critically ill patients, to allow attainment of pharmacodynamic targets for the infecting organisms considering the pharmacokinetic alterations in these patients(61).

In a systematic review study exploring the evidence available of poor quality medicines in the literature, of the 15 studies with good methodological quality conducted in low- and/or lower middle- income countries, the median prevalence of substandard/counterfeit medicines was 28.5% (range 11-48%). Majority of the studies (93%), reported drug samples with insufficient amounts of the active ingredients and especially with antimicrobials purchased from unlicensed outlets. These studies reporting high prevalence of substandard antimicrobials could inadvertently be contributing to sub therapeutic dosages in our set up especially in case of inadequate active ingredients in the antibiotics further worsening clinical outcomes, increasing rates of bacterial resistance, health care costs and morbidity and mortality(62).

2.3.5. Over-dosage

Drug overdose is deemed to have occurred if a patient takes or receives too much of an otherwise appropriate medication for his/her medical condition(1). The correct dose for any antibiotic is achieved from pharmacokinetic and pharmacodynamic studies during clinical trials. The doses must be above the minimum inhibitory concentrations for complete bacteriological cure but not too much to cause toxicity (within therapeutic limits) and must put into consideration all the patient factors, especially hepatic and renal function which are the main organs for drug metabolism and excretion, respectively(63).

Most patients with renal (and hepatic) dysfunctions almost invariably have drug dosage errors which can cause adverse drug reactions and poor clinical outcomes(64). Drugs excreted renally, and antibiotics are not an exception, require dose adjustment according to creatinine clearance or glomerular filtration rate, and online and electronic calculators are available to aid these calculations. Dosage adjustments can either be by dose reductions, dosing interval lengthening or by both methods(65). In a study done in an Indian hospital, investigating the prevalence of MRPs among patients with renal impairment, 327 MRPs were identified in 308 patients reviewed and overdose at a prevalence of 19.3% was the most common MRP. In the study, anti-infective agents came second with a prevalence of 26.3% after cardiovascular agents at 33.6%, as therapeutic classes of medications implicated in causing the MRPs(64).

In another study done at Grenoble University Hospital in France, that assessed pharmaceutical care in CKD patients, 18.3% of pharmaceutical interventions concerned drug overdose(66). An almost similar study done at KNH found out that patients with chronic kidney disease stage 4 were 4.7 times more likely to experience a drug overdose issue compared to patients with CKD stage 3(32). In another study at KNH looking into antibiotic use patterns and dose adjustments in CKD patients, it was found out that over-dosage was the most common antibiotic use problem and mainly involved ceftriaxone and amoxicillin-clavulanate, the most commonly prescribed drugs in the set up(67). Another study in Switzerland found out that patients in internal medicine wards received many drugs putting them at greater risk of DRPs that increases morbidity and mortality. Of the most frequently encountered DRPs, 16% involved over-dosage(68).

2.3.6. Failure to receive drug

Failure to receive drug (FRD) implies the inability of a patient to receive a drug for his or her medical condition due to pharmaceutical, psychological, sociological or economic reasons i.e. failure by the patient to receive a drug due to lack of an appropriate drug formulation for the indicated administration route, drug too expensive for patient to afford-where patient is required to purchase a drug for administration, patient's refusal to receive drug, lack of intravenous access, lack of intravenous access devices, lack of drug in the hospital or lack of drug administration to the patient by the doctor or nurse(1).

In a study on the determinants of non-compliance with short term antibiotic regimens, communication between the doctor and the patient affected compliance to medications(69). To achieve full therapeutic benefits from antibiotics, patients must adequately adhere to prescribed treatment regimens. Although there is no definitely agreed standard rates of adherence for full therapeutic benefit (some suggesting 80% as acceptable while others suggesting 95% rate of adherence as mandatory) it is explicit that poor adherence to medications is associated with worsening of disease, increased hospital admissions, increased health care costs and mortality(70). Better adherence to medications can be achieved through the use of less complex dosage schedules by practitioners(71).

In a study done at KNH looking at factors influencing medication administration practice among nurses at general critical care unit, delays in receiving drug orders from pharmacy, lack of medication, and increased workload on the nurses greatly affected medication administration practice, a scenario which is likely replicated in the medical wards which potentially contribute to failure to receive drugs by the patients(72).

2.3.7. Drug without indication

Drug without indication (DWI) implies the use of a drug by a patient without a justifiable medical condition(1).Unnecessary antibiotic use may occur as a result of patient expectations, physician attitudes or clinical error. In a study on treatment of sore throat by family physicians, about 67% of antibiotics prescribed were to patients with culture-negative results and were considered unnecessary. The rate of unnecessary prescribing was 5.1% (73).

In a study in Norway describing the frequency and types of DRPs in hospitalized patients, it was found out that 81% of patients enrolled in the study had DRPs, of which unnecessary drugs use comprised 16.7% (21). In another study in a USA university-affiliated hospital, in a total of 1941 days of antimicrobial therapy prescribed to 129 patients, a total of 576 (30%) of the 1941 days of therapy were deemed unnecessary. The most common reason for unnecessary therapy included administration of antimicrobials for unnecessarily longer durations (192 days of therapy), for noninfectious or nonbacterial syndromes (187 days of therapy), and treatment of colonizing or contaminating microorganisms (94 days of therapy). Anti-anaerobic agents accounted for 203 (35%) of needless antimicrobial days of therapy(18).

In yet another study to determine inappropriate fluoroquinolone prescribing patterns among admitted patients in a tertiary care and teaching hospital, of the 1773 days of fluoroquinolone therapy, 690 (39%) were deemed unnecessary. The most common reason for unnecessary therapy included administration of antimicrobials for noninfectious or nonbacterial syndromes (292 days of therapy) and administration of antimicrobials for unnecessarily longer duration (234 days of therapy). The unnecessary use of fluoroquinolones was an important risk factor for colonization and infection with fluoroquinolone-resistant gram-negative bacilli (8% of regimens) and for *clostridium difficile* infection (CDI) (4% of regimens). Besides, there was an increased incidence of gastrointestinal adverse effects (in 14% of the regimes)(74).

2.3.8. Indication without drug

Indication without drug is deemed to have occurred when a patient is not getting a medication for a confirmed medical condition(1). In a study done in KNH investigating the prevalence of MRPs among adult chronic kidney disease patients, 271 MRPs were identified and indication without drug comprised 18.1% of the cases(32).

In another study to identify and characterize DRPs experienced by patients with end stage renal disease (ESRD) on admission, and the relationship of the DRPs to gaps in medical information transfer, a total of 199 DRPs were ascertained in 47 patients who were prospectively identified and clinically assessed by a clinical pharmacist. In the study, 92% of the patients had a minimum of one DRP on admission and the most common

DRP identified was indication without drug at 51.3%. Of the total DRPs, 130 (65%) were related to breaches in medication information transfer, highlighting the significance of medical information transfer between ambulatory clinics and inpatient hospital, admitting physician and the patient, and possibly medical information transfer between the patients' clinical care team with imaging and laboratory departments on investigation requests which determine drug therapy(75).

In another study to describe the frequency and types of DRPs in hospitalized patients in five Norwegian hospitals, 81% of the patients had DRPs, and the need for additional drugs, indication without drug, comprised 19.7% of the DRPs most frequently encountered(21). In yet another study to examine drug use in a general internal medicine wards in a hospital, a total of 383 DRPs were identified, and untreated indications comprised 18% of the most frequently identified DRPs(68).

2.4. Literature gap

From the literature review, there is limited research on MRPs due to antibiotics use in medical patients in African countries, and in Kenya, despite the prevalent use of these drugs, reports of increasing local and global concern of antimicrobial resistance and consequential increased health care costs and morbidity and mortality. Though the risks of comorbid conditions and polypharmacy has been identified as significantly contributing to MRPs due to drug use in several studies, none of the studies specifically investigated the risk factors associated with MRPs due to antibiotic use.

This study aims to establish the prevalence of MRPs in patients on antibiotics in the medical wards and the associated risk factors with each category of MRP related to antibiotic use.

CHAPTER THREE: METHODOLOGY

3.1. Introduction

This chapter outlines the study design, study location, study population, sampling method, data collection tools, data collection, data management, quality assurance, data analysis methods and research execution logistics and ethical approval.

3.2. Study design

This study is a descriptive cross-sectional study. Prevalence of the various classes of MRPs in patients prescribed antibiotics in the medical wards was determined alongside likely patient and provider risk factors associated with the MRPs. For this study method, study participants were selected based on an inclusion and exclusion criteria and allowed us to measure both outcomes and exposures at the same time and consequently derive information on the prevalence of MRPs in the medical patients. This study method allows quick, economical and timely realization of the study objectives

3.3. Study location

This study was carried out in the medical wards of Kenyatta National Hospital, KNH. Kenyatta National Hospital is Kenya's, and the regions' top largest public tertiary care teaching and referral hospital, located at Nairobi. It offers teaching needs for the University of Nairobi's College of Health Sciences, and other medical institutions in the region. It has a bed capacity of 1800 spread out in 50 wards, and over 22 outpatient clinics (ctrl + click) Kenyatta National Hospital Information .

Medical patients referred to the institution are admitted in wards 7A to 7D and wards 8A to 8D. Physicians, surgeons, nurses, pharmacists, nutritionists, amongst other health care staff, comprise the multidisciplinary clinical teams involved in the care of the admitted patients.

3.4. Study population

The study population comprised adult patients prescribed antibiotics, and admitted in the medical wards at KNH over the study period from November to December, 2018.

3.5. Eligibility criteria

3.5.1. Inclusion criteria

Patients who were eighteen years or older and prescribed antibiotic(s) while admitted in the medical wards (including those in the medical wards' mini ICUs) and who by themselves or through their proxies, consented to the study after being fully informed about the study, met the inclusion criteria for the study. Any patient, eighteen years old or above, who also had an unmet need for an antibiotic, as agreed to by the attending physician(s) after consultation by the study personnel was also eligible for the study. Other than this, all patients who were eighteen years or older, and admitted in the medical wards (including those in the medical wards mini ICUs) and whose reason for their admission was because of an adverse drug reaction possibly due to antibiotic use, and not attributable to other drugs in the medication history, were also included in the study, if they consented.

3.5.2. Exclusion criteria

Patients who were excluded from this study,either: were less than eighteen years of age, did not consent to the study, or had no prescribed antibiotic or an omitted need for an antibiotic.

3.6. Sample size

The sample size for this study was based on the estimate of 96.7% (17) as the prevalence of medication related problems among patients in the medical wards at KNH.

Applying Fischer's formula, sample size was calculated thus (76);

$$\mathbf{n} = \frac{\boldsymbol{Z^2\alpha/2}\ \boldsymbol{p(1-p)}}{\delta^2}$$

Where;

n= Desired sample size.

P= Estimated prevalence of 96.7% of the outcome (MRPs) in the medical wards of KNH(17).

$\boldsymbol{Z^2\alpha/2}$ = The square of the standard normal deviate that cuts off an area α at the

tails (2 sided). **Z**= 1.96 for 95% confidence level.

δ = Margin of error/desired level of precision. Set at 5% (0.05).

$$\mathbf{n} = \frac{\mathbf{1.96^2}\alpha/2 \quad \mathbf{0.967(1-0.967)}}{0.05^2}$$

n= 49

The sample size for the study was therefore set at a minimum of 49 patients.

3.7. Sampling method

Participants for the study were systematically selected from the list of patients admitted to the medical wards. Each of the eight medical wards (7A-7D and 8A- 8D) is categorized into cubes/sections designated as White, Blue and Green for both males and females and a common mini ICU per ward. To obtain a sample that was representative of all the medical wards, participants who met the eligibility criteria were selected from each of the seven sections of the eight medical wards using a pre-structured recruitment eligibility form (appendix 1). This was done by pre-selecting every even numbered patient from the list of admitted patients per section kept by the ward-in- charge/health records information officer, and consecutively until an eligible participant was found, and those who met the inclusion criteria were recruited for the study.

Preselected study participants who hadn't been prescribed antibiotics, on checking their charts, were dropped and the consecutive even numbered patient in the respective list was selected for the recruitment process. However if chart information pointed towards the need for an antibiotic by the patient, the study personnel liaised with the patient's attending clinical team and where there was an agreed omitted need for an antibiotic, the study participant was still recruited for the study as this indicated indication without drug (IWD). This study participant recruitment method gave a sample of 94 patients which is above the minimum calculated study sample size of 49 for the study.

All recruited participants or their proxies (patient proxy is the patients' caregiver/relative of adult age who can make decisions on behalf of the patient) then had an explanation of the study purpose, benefits and harms, and assurance of confidential handling of their data/patients data (in case of caregiver) by using a consent explanation form (Appendix

2). Patients who couldn't comprehend English had interpretation of the consent explanation form details into Kiswahili language by the study personnel or their mother tongue through the help of a staff who understood the participants' mother tongue. Where the participant was too ill, proxies were used to explain the study details.

All patients or their proxies who consented to participate in the study then acknowledged their agreement to participate in the study by signing the consent declaration (Appendix 2).

3.8. Data collection tools

3.8.1 Data extraction form

A data extraction tool/questionnaire (Appendix 3) was then used to collect relevant information from the study patients and their charts. This was a structured form with three sections; the first section was a questionnaire administered to the patient, or their proxies, to obtain the patient's socio demographic details, chief complaint, history of present illness, past medical history, medication history, social history, review of systems and MRPs as reported by the patient. The second section involve abstraction of the patient's medication record and chart review details noting the recorded chief complain, history of present illness, past medical history, medication history, social history, review of systems, relevant investigations ordered, working diagnosis, comorbidities, prescribed drugs (dosage, frequency and duration). The third section was used for evaluation, classification, severity assessment and identification of cause(s) of the various MRPs present. Where clarification or further inquiry was needed, or where a concerning MRP was identified, the study personnel liaised with the patient or the patients' clinical care team for the clarification/further information and or appropriate intervention.

3.8.2 Informed consent

The need for informed consent was obtained from the patient, or their proxy, and declared through signing of the consent declaration form (Appendix 2) before any information was abstracted from the patient or patients' charts.

3.9. Data collection

Data was collected over the months of November and December and involved patient

interview and data abstraction, with the help of study personnel, from the recruited patients and their charts.

Relevant information for the study as outlined in the data collection form was abstracted through questionnaires and medical chart review for each patient and accordingly recorded in the data collection tool. MEDSCAPE clinical information software (MEDSCAPE®, 2017) and KNH guide to empiric antimicrobial therapy (second edition, 2018) was utilized in clinical decision making in evaluating for the presence or absence of the MRPs and severity assessment.

3.10. Variables

Both descriptive and inferential statistics were used to describe the population data and make predictions of likely association between the variables. The main outcome variable was MRP prevalence in patients prescribed antibiotics in the medical wards at KNH. The various MRP classes as outlined by Helper and Strand (1), and defined in the literature review, were the outcome variables for this study and were determined as follows;

3.10.1 Adverse drug reactions

In this study, ADRs were documented patient complaints or deranged laboratory results, which occurred after initiation of the antibiotic, and attributable to the antibiotic(s) prescribed in the correct doses for the medical condition. Examples of possible ADRs include allergic skin drug reactions e.g. Stevens Johnson Syndrome (SJS), electrolyte disturbances of potassium, chloride, and sodium and gastrointestinal disturbances which manifested as either diarrhea, nausea and vomiting or abdominal pain.

3.10.2 Drug interactions

Drug interactions were evaluated by use of MEDSCAPE®, 2017 drug interaction checker. Drug-drug interactions were only evaluated and documented. This involved keying in all the prescribed drugs and checking for interactions using the interaction checker. Only significant and serious drug-drug interactions as highlighted by the interaction checker classification were documented. All serious interactions that warranted change of regimen, or dose modification, or concomitant drug-drug use contraindications, were reported to the patient's attending physician.

3.10.3 Improper drug selection

Improper drug selection was deemed to have occurred if the antibiotic choice did not conform to the KNH guide to empiric antimicrobial therapy (second edition, 2018) or laboratory susceptibility tests, if any was ordered. The use of an antibiotic without consideration of the patient's concomitant conditions was regarded as improper drug selection. For example, use of a nephrotoxic antibiotic in a patient with impaired renal function and especially where safer alternatives exist for the treatment of the bacterial infection. Any antibiotic use where there was a contraindication was also considered as an IDS.

3.10.4 Sub therapeutic dosage

Sub therapeutic dosage was considered when the drug dose for a particular medical condition was incorrect in regards to the recommended frequency and duration. All doses that didn't meet the recommended frequency and duration were regarded as STD e.g. the recommended dosage and duration for cotrimoxazole use in treatment of Jiroveci pneumonia is 15-20mg per kilogram/day based on the trimethoprim component divided every 6 or 8 hours for 21 days (MEDSCAPE®, 2017). All dosage modifications due to renal/hepatic impairment were also factored in regarding the dose as sub therapeutic or not.

3.10.5 Over dosage

Over dosage was regarded where the prescribed antibiotic dose was high as regards part of or all of the dose components-dose, frequency and duration. Failure to factor in renal/hepatic impairment dose modifications was also treated as an overdose, so was incorrect dose adjustments that was still high as per clinical recommendations.

3.10.6 Failure to receive drug

Failure to receive drug was documented where the patient didn't get the prescribed medication either due to drug unavailability or where the nurse didn't administer the medication e.g. when the patients intravenous access line was not fixed for a patient who had been prescribed an IV medication. Patients who declined medications were also documented here.

3.10.7 Drug without indication

Where a patient had been prescribed an antibiotic without a valid medical condition was regarded as DWI. This especially if clinical or laboratory tests didn't point to any possible bacterial infection. And where multiple antibiotics had been prescribed, and one of the additional antibiotics didn't confer additional bacterial coverage but less coverage than another concomitantly administered antibiotic, this antibiotic was documented as a DWI.

3.10.8 Indication without drug

Where a patient was not receiving an antibiotic where there was a documented bacterial infection was regarded as an IWD. This also included where there was need for prophylaxis and the recommended antibiotic was not prescribed.

Table 3.1: Predictor variables (Covariates)

	Variable	**Class**
Patient factors	Age	Discrete
	Gender	Binary
	Marital status	Binary
	Education level	Binary
	Employment status	Binary
	Occupation	Binary
	Smoking	Binary
	Alcohol intake	Binary
Regimen and comorbidity status	Number of medications	Discrete
	Number of comorbidities	Discrete
	Diabetes mellitus	Binary
	Hypertension	Binary
	Anaemia	Binary
	Human immunodeficiency Virus	Binary
	Kidney disease§	Binary
	Liver disease¶	Binary
	Respiratory disease*	Binary
	Heart Disease ħυ	Binary
	Gastrointestinal disease σι	Binary
	Cancersզ	Binary

KEY;

§ Encompassed all kidney diseases (except cancers) e.g. acute kidney injury, chronic kidney disease, nephrotic syndrome etc.

¶ Included all liver disease e.g. drug or viral hepatitis except liver cancer(s) etc.

*Included all respiratory diseases (except cancer) e.g. TB, COPD, asthma, etc.

ћ All heart diseases, except cancer, e.g. Heart failure, Congestive cardiac failure, etc.

σ Included gastrointestinal diseases, excluding cancers e.g. peptic ulcer disease and gastritis.

ɖ Cancers of any body organ or tissue were noted here.

3.11. Data management

Data were collected through standard data collection form outlined above. To ensure protection of patient confidentiality, data collection was done in the wards and hospital patient records identifiers were not recorded in the data collection forms but only unique codes generated and known only to the investigator. Collected data was entered into a Microsoft excel file with password protection and stored in a password protected computer. All the raw data were safely kept under lock and key and could only be accessed by the principal investigator and by the supervisors or KNH/UoN ERC upon demand.

Data entry, coding, cleaning and processing was done at the end of each data collection day by the chief investigator, and backed up in an external hard drive which was separately safely stored away from the computer where data had initially been input.

All data collected for the purposes of the study and contained in the data collection forms, the study computer or external hard drive will be permanently deleted at the end of the study after satisfactory analysis and paper publication.

3.12. Quality assurance

Data collected by the study personnel was reevaluated for correctness by the principal investigator during data entry. Good Clinical Practice (GCP) standards and International

Council for Harmonization (ICH) guidelines were adhered to in data handling.

3.12.1 Validity

The sample size for the study was 94 patients which is roughly one-and-half times the proportion of patients prescribed antibiotics in the medical wards according to Okiko's study,2017(16). This sample size was therefore representative of patients prescribed antibiotics in the medical wards and ensure external validity. Internal validity was ensured through clear variable definition to limit confounding variables.

3.12.2 Reliability

Data was tested for ambiguities and reproducibility using the first fifteen patients and any discrepancies corrected to ensure consistent, reliable and reproducible data.

3.13. Data analysis

Descriptive statistics were used to summarize the data. The mean and standard deviation (SD) and the median and inter quartile range (IQR) were used to summarize continuous variables (age, and body weight) and discrete variables (number of antibiotics used, number of drugs used, and number of MRPs among others) if the Gaussian assumptions were satisfied. The normal distribution assumptions were assessed using Shapiro and Wilks' test for normality.

The prevalence of MRPs due to antibiotics, and due to other drugs were summarized and the frequency of prevalence of MRPs divided by the total number of participants included in the study computed.

Association between the occurrence of MRPs due to antibiotics and categorical variables were assessed using Chi Square test. Fisher's exact test was used whenever the Chi Square assumptions were violated. Wilcoxon rank sum test (Mann-Whitney U test) was used to compare the medians while independent samples t-test was used to compare the means between those who had MRPs due to antibiotics use and those who did not have.

Logistic regression model was used to assess the factors associated with occurrence of MRPs due to antibiotics use. We found out that marital status, estimated glomerular filtration rate ranges, use of ceftriaxone, and use of ceftazidime were significantly associated with occurrence of MRPs due to use of antibiotics. These variables were

included in the multivariate logistic regression model to assess their joint effect on the occurrence of MRPs due to use of antibiotics. The factors associated with the outcome (MRPs) were selected using backward selection method. This is where we include all the variables significant in the bivariate analysis into the multivariate analysis model. Then the variables that have the greatest p-value > 0.05 are removed one at a time until a parsimonious model was achieved. We reported the odds ratios (OR) and corresponding 95% confidence intervals (95% CI).

Results were then presented using tables, figures and graphs.

Data analysis was done using STATA 13 SE (77845 College Station Texas USA).

3.14. Ethical considerations

Before commencement of the study, approval was obtained from KNH/UoN ERC and Kenyatta National Hospital administration. Ethical research principles as outlined in the Nuremberg Code and the Declaration of Helsinki were adhered to.

3.14.1 Informed consent

Informed consent for this study was obtained from the patient, or their proxy, before any information was collected from the patient or their charts. Patient proxy was the patients' caregiver/relative of adult age who could make decisions on behalf of the patient. Proxies were used where communication barrier existed between the study personnel and the patient e.g. in case of unconscious patient(s), demented patients or patients who failed to cognitively understand the scope of the study. The proxy was required to acknowledge authority to represent the patient, completely understand the purpose of the study, and voluntarily, knowingly and competently agree to represent the patient in the study. All relevant data was abstracted from the patient and their medical charts and any necessary interventions were done through the respective patients' attending clinical teams.

3.14.2 Risks and benefits

There were no risks to the patients as data for the study was only obtained through patient interviews and data abstraction from the patients' medical charts with no further need for any procedures to the patients unless where there was a need for further laboratory investigations to rule out an MRP as agreed to by the patients' responsible clinical team.

Most importantly, the quality of care for the patients and their clinical outcomes was likely improved as any harmful or potentially harmful MRP(s) identified during the study was promptly relayed to the patient's attending physician for evaluation and correction. Patient confidentiality was maintained through the use of unique codes known only to the principal investigator and by safe data storage.

CHAPTER FOUR: RESULTS

4.1. Socio-demographic characteristics of the study participants.

A total of 94 participants were included in the study. The median age was 41.0 (IQR: 35.0, 55.3) years with a range of 18.0 to 85.0 years (Table 4.1). The median weight was 63.0 (IQR: 56.3, 71.0) kilograms with a range of 34.0 to 125.0 kilograms. Up to 39.4% were male, 36.2% were single, 67.0% were unemployed, and 60.1% had a secondary or tertiary level of education. Up to 45.7% have ever used alcohol, and 11.7% have ever smoked.

Table 4.1: Socio-demographic characteristics

Variable N=94	**Median (IQR) or n (%)**
Age (Years), Median (IQR)	41.0 (35.0 ,55.3)
Range (Min. - Max.)	18.0 – 85.0
Gender, n (%)	
Male	37 (39.4%)
Female	57 (61.3%)
Weight (Kg), Median (IQR)	63.0 (56.3 ,71.0)
Range (Min., Max.)	34.0 – 125.0
Marital Status, n (%)	
Single	34 (36.2%)
Married	60 (63.8%)
Occupation, n (%)	
Unemployed	63 (67.0%)
Employed	31 (33.0%)
Education level, n (%)	
None	7 (7.4%)
Primary	29 (31.2%)
Secondary	33 (35.9%)
Tertiary	22 (24.2%)
Ever used alcohol, n (%)	
No	51 (54.3%)
Yes	43 (45.7%)
Ever smoked cigarettes, n (%)	
No	83 (88.3%)
Yes	11 (11.7%)

4.2. Comorbidities

The comorbidities among the study participants are depicted in figure 4.1 below.

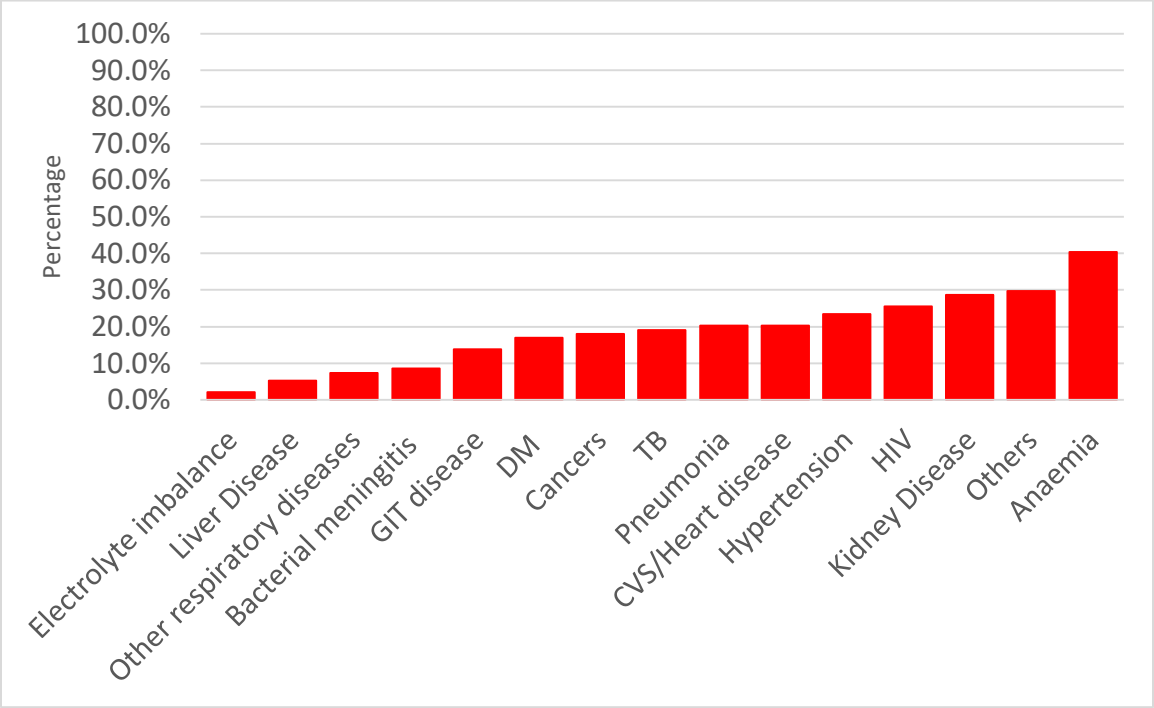


Figure 4.1: Distribution of the occurrence of comorbidities

Anemia, 38 (40.4%) was the most prevalent comorbidity followed by kidney disease, 27 (28.7%), and HIV, 24 (25.5 %). Other diseases, 28 (29.8%) comprised a collection of cellulitis, schizophrenia, hypothyroidism, tinea corporis, pancreatitis, skin disease, systemic lupus erythematosus, sepsis, drug reaction, candidiasis, diabetic foot, testicular swelling, alcoholism, psychosis, splenomegaly, peripheral neuropathy, urinary tract infection and depressive disorder. The other respiratory diseases included; asthma, pneumocystis Jiroveci pneumonia and chronic pulmonary obstructive disease. Sixty four (68.1%) and 11 (11.7%) participants had creatinine clearance of >50mL/min and < 15mL/min respectively, while 14 (14.9%) and 5 (5.3%) had creatinine clearance rates ranging between 31-49mL/min and 15-30mL/min respectively. The median number of comorbidities was 3 (IQR: 2, 3) with a minimum and a maximum of 1 and 5 respectively.

4.3. Prevalence of MRPs due to antibiotics

Table 4.2 depicts the summary of prevalence of antibiotic use by antibiotic classes.

Table 4.2: Classes of antibiotic prescribed (n=94)

Class of antibiotic	**n (%)**
Cephalosporins	49 (52.1%)
Penicillins	23 (24.5%)
Antimycobacterials	18 (19.1%)
Sulphonamides	18 (19.1%)
Nitroimidazoles	11 (11.7%)
Macrolides	9 (9.6%)
Fluoroquinolones	8 (8.5%)
Lincosamides	7 (7.4%)
Carbapenems	4 (4.3%)
Topical	3 (3.2%)
Aminoglycosides	3 (3.2%)
Glycopeptides	2 (2.1%)
Tetracyclines	2 (2.1%)
Nitrofurans	1 (1.1%)

Majority of the participants used cephalosporins, 49 (52.1%), followed by penicillins, 23 (24.5%), antimycobacterials, 18 (19.1%), sulphonamides, 18 (19.1%), and nitroimidazoles, 11 (11.7 %).

Table 4.3: Specific antibiotics prescribed (n=94)

Antibiotic	**n (%)**
Ceftriaxone	31 (33%)
Amoxicillin-clavulanate	19 (20.2%)
Rifampin	18 (19.1%)
Isoniazid	18 (19.1%)
Cotrimoxazole	18 (19.1%)
Ceftazidime	16 (17%)
Ethambutol	14 (14.9%)
Pyrazinamide	13 (13.8%)
Metronidazole	11 (11.7%)
Clarithromycin	8 (8.5%)
Clindamycin	7 (7.4%)
Ciprofloxacin	6 (6.4%)
Gentamicin	3 (3.2%)
Meropenem	3 (3.2%)
Flucloxacillin	3 (3.2%)
Cefuroxime	2 (2.1%)
Vancomycin	2 (2.1%)
Levofloxacin	2 (2.1%)
Piperacillin-Tazobactam	2 (2.1%)
Silver sulfadiazine	2 (2.1%)
Imipenem-cilastatin	1 (1.1%)
Azithromycin	1 (1.1%)
Doxycycline	1 (1.1%)
Tigecycline	1 (1.1%)
Nitrofurantoin	1 (1.1%)
Pyrimethamine	1 (1.1%)
Sulfadiazine	1 (1.1%)
Mupirocin ointment	1 (1.1%)

The most commonly prescribed antibiotics (Table 4.3) were ceftriaxone, 31 (33%), followed by amoxicillin-clavulanate, 19 (20%), rifampin, 18 (19.1%), isoniazid, 18 (19.1%), cotrimoxazole, 18 (19.1%), ceftazidime, 16 (17%), ethambutol, 14 (14.9%) and pyrazinamide, 13 (13.8%).

Table 4.4: Distribution of the number of antibiotics and other drugs used

Variable **N=94**	**Median (IQR) or n (%)**
Total number of antibiotics, Median (IQR) Range (Min., Max.)	2 (1 , 2) 0 - 9
Total number of drugs, Median (IQR) Range (Min., Max.)	8 (5 , 10) 1 - 14

The median number of antibiotics used per participant was 2 (IQR: 1, 2) and the maximum number was nine. The median number of total drugs (antibiotics and non-antibiotics) prescribed to each participant was 8 (IQR: 5, 10) with a minimum of 1 and a maximum of 14.

4.4 Overall prevalence of MRPs due to antibiotics use.

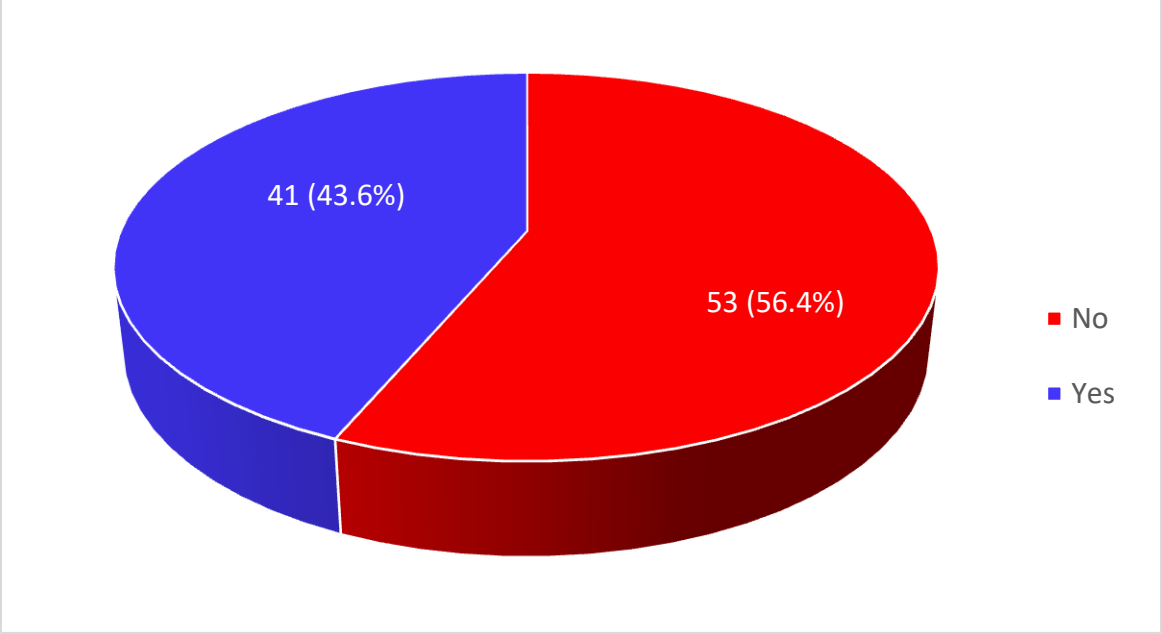


Figure 4.2: Overall prevalence of MRPs due to antibiotic use

The maximum number of reported MRPs per participant was 4, with 41 (43.6 %) (Figure 4.2) having at least one MRP. Nine participants had two MRPs and three MRPs were observed in two participants while one had four MRPs.

Table 4.5: Prevalence of MRPs due to antibiotics (n=94)

Medication related problem	**n (%)**
Drug-drug interactions	13 (13.8%)
Wrong drug	13 (13.8%)
Over dosage	12 (12.8%)
Adverse drug reaction	6 (6.4%)
Sub-therapeutic dosage	6 (6.4%)
Failure to receive drug	3 (3.2%)
Indication without drug	2 (2.1%)
Drug without indication	2 (2.1%)

The most reported MRPs were drug-drug interactions, 13 (13.8%) and wrong drug, 13 (13.8%). Over dosage was next in the rank with 12 (12.8%) participants reported to have experienced this problem. Other MRPs included adverse drug reaction, 6(6.4%), sub-therapeutic dosage, 6 (6.4%), failure to receive drugs, 3 (3.2%), indication without drug, 2 (2.1%), and drug without indication, 2 (2.1 %) (Table 4.5).

Table 4.6: Prevalence and severity of MRPs due to antibiotic use (n=94)

Variable	**n (%)**
Number of MRPs due to antibiotics	
0	53 (56.4%)
1	29 (30.9%)
2	9 (9.6%)
3	2 (2.1%)
4	1 (1.0%)
MRP severity	
Mild	7 (7.5%)
Moderate	32 (34%)
Severe	2 (2.1%)
Fatal	0 (0%)

Table 4.7: Identified causes of MRPs due to antibiotics use (n=94)

MRP	n (%)
Inappropriate prescribing	32 (34%)
Drug idiosyncrasy	14 (14.9%)
Inappropriate monitoring	3 (3.2%)

The main cause of MRPs (Table 4.7) was inappropriate drug prescriptions, 32 (34.0%) followed by drug idiosyncrasy, 14 (14.9%) then inappropriate monitoring, 3 (3.2%). Drug idiosyncrasy refers to an abnormal physical reaction to drug (or food) by a patient resulting in signs and/or symptoms(1).

4.5. MRPs due to non-antibiotics use

Medication related problems due to other drugs other than antibiotics were also assessed. The findings are summarized in table 4.8 depicting the prevalence of MRPs due to non-antibiotics use, table 4.9 depicting the identified causes of MRPs due to non-antibiotic drug use, and table 4.10 depicting severity of identified MRPs due to non-antibiotic use.

Table 4.8: Prevalence of MRPs due to non-antibiotic use (n=94).

Variable	n (%)
Indication without drug, (n %)	7 (7.4%)
Over dosage, (n %)	7 (7.4%)
Failure to receive drug, (n %)	4 (4.3%)

Table 4.9: Identified causes of MRPs due to non-antibiotic use (n=94).

Variable	n (%)
Inappropriate Prescribing	11 (11.7%)
Inappropriate monitoring	5 (5.3 %)
Inappropriate behavior by the patient	2 (2.1 %)

Table 4.10: Severity of identified MRPs due to non-antibiotic use (n=94).

Variable	n (%)
Number of MRPs due to non-antibiotics	
0	78 (83%)
1	14 (14.9%)
2	2 (2.1%)
Severity of MRPs due to non-antibiotics	
Mild	4 (4.3%)
Moderate	9 (9.6%)
Severe	3 (3.2%)
Fatal	0 (0%)

The maximum number of reported non-antibiotic associated MRPs for the participants was 2 with 17% of the study participants having at least one non-antibiotic associated MRP (Table 4.10).

The main cause of MRPs due to non-antibiotic drug use was inappropriate prescribing, 11 (11.7%). Other causes were inappropriate monitoring, 5 (5.3%), and inappropriate behavior by the patient, 2 (2.1%). Inappropriate behavior by the patient refers to the patient's refusal to receive prescribed drugs without any specific reasons, which essentially results in non-compliance.

There were 3.2% of the participants who experienced severe MRPs due to non-antibiotic drugs.

4.6. Factors associated with antibiotic related MRPs

4.6.1 Association between antibiotic related MRPs and socio-demographic characteristics.

Factors associated with prevalence of antibiotic related MRPs were assessed using chi square, Fischer's exact test and Wilcoxon rank sum test where applicable.

The association between the prevalence of MRPs due to antibiotics and socio-demographic characteristics are summarized in table 4.11.

Table 4.11: Association between antibiotic related MRPs and socio-demographic characteristics

Characteristics	Presence of MRPs due to antibiotic use		
	No (n, %)	**Yes (n, %)**	**P-value**
Age (Years), Median (IQR)	39.0 (35.0, 52.0)	42.0 (34.0, 56.0)	0.425
Gender			
Male	19 (51.4%)	18 (48.7%)	
Female	34 (59.7%)	23 (40.4%)	0.428
Weight (Kg), Median (IQR)	63.0 (57.0, 71.0)	63.0 (53.0, 68.0)	0.434
Marital Status			
Single	14 (41.2%)	20 (58.8%)	
Married	39 (65.0%)	21 (35.0%)	**0.025**
Occupation			
Unemployed	36 (57.1%)	27 (42.9%)	
Employed	17 (54.8%)	14 (45.1%)	0.832
Education level			
None	4 (57.1%)	3 (42.9%)	
Primary	12 (41.4%)	17 (58.6%)	
Secondary	23 (65.7%)	12 (34.3%)	0.248
Tertiary	14 (60.9%)	9 (39.1%)	
Alcohol, n (%)			
No	21 (48.8%)	22 (51.2%)	
Yes	32 (62.8%)	19 (37.3%)	0.176
Smoking, n (%)			
No	5 (45.5%)	6 (54.5%)	
Yes	48 (57.8%)	35 (42.2%)	0.437

There was a statistically significant relationship between marital status and prevalence of MRPs (**p=0.025**).Those who were married had lower prevalence of MRPs compared to those who were single (35.0% vs. 58.8%).

There was no statistically significant association between the MRPs and the other socio-demographic characteristics.

4.6.2 Association between antibiotic related MRPs and creatinine clearance.

Fisher's exact test was applied in determining the association (Table 4.12). The prevalence of MRPs significantly increased with a decrease in the rate of estimated glomerular filtration rate (**p = 0.016**).

Table 4.12: Association between antibiotic related MRPs and creatinine clearance.

	Presence of MRPs due to antibiotic use		
Variable	**No**	**Yes**	P-value
CrCL >50, n (%)	43 (67.2%)	21 (32.8%)	
CrCL 31-49, n (%)	5 (35.7%)	9 (64.3%)	
CrCL 15-30, n (%)	2 (40.0%)	3 (60.0%)	**0.016**
CrCL <15, n (%)	3 (27.3%)	8 (72.7%)	

4.6.3. Association between classes of antibiotics and antibiotic related MRPs

Chi-square test and Fisher's exact test, where appropriate, were applied in determining the association between prevalence of MRPs and class of antibiotics (Table 4.13).There was sufficient evidence (where $p<0.05$) to support the difference in the prevalence of MRPs between those who were treated using carbapenems (**p= 0.033**) compared to those treated with the other classes of antibiotics.

Table 4.13: Association between classes of antibiotics and antibiotic related MRPs.

		Presence of MRPs due to antibiotic use		
Variable		**No n (%)**	**Yes n (%)**	**P-value**
Cephalosporins	No	25 (54.4%)	21 (45.7%)	
	Yes	28 (58.3%)	20 (41.7%)	0.697
Penicillins	No	38 (53.5%)	33 (46.5%)	
	Yes	15 (65.2%)	8 (34.8%)	0.326
Antimycobacterials	No	43 (56.6%)	33 (43.4%)	
	Yes	10 (55.6%)	8 (44.4%)	0.937
Sulphonamides	No	44 (57.9%)	32 (42.1%)	
	Yes	9 (50.0%)	9 (50.0%)	0.544
Nitroimidazoles	No	46 (55.4%)	37 (44.6%)	
	Yes	7 (63.6%)	4 (36.4%)	0.428
Macrolides	No	48 (56.5%)	37 (43.5%)	
	Yes	5 (55.6%)	4 (44.4%)	0.613
Lincosamides	No	48 (55.2%)	39 (44.8%)	
	Yes	5 (71.4%)	2 (28.6%)	0.337
Fluoroquinolones	No	50 (57.5%)	37 (42.5%)	
	Yes	3 (42.9%)	4 (57.1%)	0.358
Carbapenems	No	53 (58.9%)	37 (41.1%)	
	Yes	0 (0.0%)	4 (100.0%)	**0.033**
Topical	No	52 (57.1%)	39 (42.9%)	
	Yes	1 (33.3%)	2 (66.7%)	0.404
Aminoglycosides	No	52 (57.1%)	39 (42.9%)	
	Yes	1 (33.3%)	2 (66.7%)	0.404
Glycopeptides	No	53 (57.6%)	39 (42.4%)	
	Yes	0 (0.0%)	2 (100.0%)	0.188

Tetracyclines	No	53 (57.6%)	39 (42.4%)	
	Yes	0 (0.0%)	2 (100.0%)	0.188
Nitrofurans	No	53 (57.0%)	40 (43.0%)	
	Yes	0 (0.0%)	1 (100.0%)	0.436

4.6.4. Association between specific types of antibiotics and prevalence of MRPs due to antibiotics

Chi Square test and Fisher's Exact test, were used, where appropriate, in determining the association. (Table 4.14). The results showed that there was statistical evidence that the participants who were on ceftriaxone had a lower prevalence of MRPs associated with the use of the antibiotic compared to those who were on the other types of antibiotics, 25.8% vs. 52.4%, (**p = 0.015).**

Table 4.14: Association between specific types of antibiotics and prevalence of MRPs due to antibiotics

		Presence of MRPs due to antibiotic use		
Variable		**No n (%)**	**Yes n (%)**	**P-value**
Ceftriaxone	No	30 (47.6%)	33 (52.4%)	
	Yes	23 (74.2%)	8 (25.8%)	**0.015**
Amoxicillin-clavulanate	No	41 (54.7%)	34 (45.3%)	
	Yes	12 (63.2%)	7 (36.8%)	0.505
Rifampin	No	43 (56.6%)	33 (43.4%)	
	Yes	10 (55.6%)	8 (44.4%)	0.937
Isoniazid	No	43 (56.6%)	33 (43.4%)	
	Yes	10 (55.6%)	8 (44.4%)	0.937
Cotrimoxazole	No	44 (57.9%)	32 (42.1%)	
	Yes	9 (50.0%)	9 (50.0%)	0.544
Ceftazidime	No	50 (64.1%)	28 (35.9%)	
	Yes	3 (18.8%)	13 (81.3%)	**0.001**
Ethambutol	No	46 (57.5%)	34 (42.5%)	
	Yes	7 (50.0%)	7 (50.0%)	0.406

Pyrazinamide	No	46 (56.8%)	35 (43.2%)	
	Yes	7 (53.9%)	6 (46.2%)	0.843
Metronidazole	No	46 (55.4%)	37 (44.6%)	
	Yes	7 (63.6%)	4 (36.4%)	0.428
Clarithromycin	No	48 (55.8%)	38 (44.2%)	
	Yes	5 (62.5%)	3 (37.5%)	0.509
Clindamycin	No	48 (55.2%)	39 (44.8%)	
	Yes	5 (71.4%)	2 (28.6%)	0.337
Ciprofloxacin	No	51 (58.0%)	37 (42.1%)	
	Yes	2 (33.3%)	4 (66.7%)	0.226
Gentamicin	No	52 (57.1%)	39 (42.9%)	
	Yes	1 (33.3%)	2 (67.7%)	0.404
Meropenem	No	53 (58.2%)	38 (41.8%)	
	Yes	0 (0.0%)	3 (100.0%)	0.080
Flucloxacillin	No	51 (56.0%)	40 (44.0%)	
	Yes	2 (66.7%)	1 (33.3%)	0.596
Cefuroxime	No	51 (55.4%)	41 (44.6%)	
	Yes	2 (100.0%)	0 (0.0%)	0.315
Vancomycin	No	53 (57.6%)	39 (42.4%)	
	Yes	0 (0.0%)	2 (100.0%)	0.188
Levofloxacin	No	52 (56.5%)	40 (43.5%)	
	Yes	1 (50.0%)	1 (50.0%)	0.685
Piperacillin-Tazobactam	No	52 (56.5%)	40 (43.5%)	
	Yes	1 (50.0%)	1 (50.0%)	0.685
Silver sulfadiazine	No	52 (56.5%)	40 (43.5%)	
	Yes	1 (50.0%)	1 (50.0%)	0.685
Imipenem-Cilastatin	No	53 (57.0%)	40 (43.0%)	
	Yes	0 (0.0%)	1 (100.0%)	0.436
Azithromycin	No	53 (7.0%)	40 (43.0%)	

	Yes	0 (0.0%)	1 (100.0%)	0.436
Doxycycline	No	53 (57.0%)	40 (43.0%)	
	Yes	0 (0.0%)	1 (100.0%)	0.436
Tigecycline	No	53 (57.0%)	40 (43.0%)	
	Yes	0 (0.0%)	1 (100.0%)	0.436
Nitrofurantoin	No	53 (57.0%)	40 (43.0%)	
	Yes	0 (0.0%)	1 (100.0%)	0.436
Pyrimethamine	No	53 (57.0%)	40 (43.0%)	
	Yes	0 (0.0%)	1 (100.0%)	0.436
Sulfadiazine	No	53 (57.0%)	40 (43.0%)	
	Yes	0 (0.0%)	1 (100.0%)	0.436
Mupirocin ointment	No	53 (57.0%)	40 (43.0%)	
	Yes	0 (0.0%)	1 (100.0%)	0.436

On the other hand, the participants who were on ceftazidime had a higher prevalence of MRPs associated with the use of the antibiotic compared to those who were on the other types of antibiotics, 81.3% vs. 35.9%, (**p =0.001)**.

There was no evidence of any difference in the rate of occurrence of MRPs due to use of other types of antibiotics, $p>0.05$.

4.6.5. Association between comorbidities and presence of MRPs due to antibiotics

The findings showed no statistically significant difference in the prevalence of MRPs between the participants who had and those who did not have comorbidities such as GIT disease, DM, cancers, TB, hypertension, pneumonia, bacterial meningitis, anemia, liver disease, and HIV among others (Table 4.15). However, there was strong evidence that the participants who had kidney disease had a higher prevalence of MRPs compared to those who were not diagnosed with kidney disease, 66.7% vs. 34.3%, (**p = 0.004)**.

Table 4.15: Association between comorbidities and presence of MRPs due to antibiotics.

Variable		Presence of MRPs due to antibiotic use		
		No	**Yes**	**P-value**
GIT disease, n (%)	No	46 (56.8%)	35 (43.2%)	
	Yes	7 (53.9%)	6 (46.2%)	0.843
DM, n (%)	No	42 (53.9%)	36 (46.2%)	
	Yes	11 (68.8%)	5 (31.3%)	0.273
Cancers, n (%)	No	45 (58.4%)	32 (41.6%)	
	Yes	8 (47.1%)	9 (52.9%)	0.392
TB, n (%)	No	43 (56.6%)	33 (43.4%)	
	Yes	10 (55.6%)	8 (44.4%)	0.937
Pneumonia, n (%)	No	40 (53.3%)	35 (46.7%)	
	Yes	13 (68.4%)	6 (31.6%)	0.236
CVS/Heart disease, n (%)	No	40 (53.3%)	35 (46.7%)	
	Yes	13 (68.4%)	6 (31.6%)	0.236
Electrolyte imbalance, n (%)	No	52 (56.5%)	40 (43.5%)	
	Yes	1 (50.0%)	1 (50.0%)	0.854
Hypertension, n (%)	No	41 (56.9%)	31 (43.1%)	
	Yes	12 (54.6%)	10 (45.5%)	0.843
HIV, n (%)	No	42 (60.0%)	28 (40.0%)	
	Yes	11 (45.8%)	13 (54.2%)	0.227
Kidney Disease, n (%)	No	44 (65.7%)	23 (34.3%)	
	Yes	9 (33.3%)	18 (66.7%)	**0.004**
Anaemia, n (%)	No	33 (58.9%)	23 (41.1%)	
	Yes	20 (52.6%)	18 (47.4%)	0.546
Liver Disease, n (%)	No	49 (55.5%)	40 (44.9%)	
	Yes	4 (80.0%)	1 (20.0%)	0.274
Other respiratory diseases, n (%)	No	51 (58.6%)	36 (41.4%)	
	Yes	2 (28.6%)	5 (71.4%)	0.123
Bacterial meningitis, n (%)	No	47 (54.7%)	39 (45.4%)	
	Yes	6 (75.0%)	2 (25.0%)	0.267
Others, n (%)	No	41 (62.1%)	25 (37.9%)	
	Yes	12 (42.9%)	16 (57.1%)	0.085
Total number of conditions/comorbidities, Median (IQR)		3 (2, 3)	3 (2, 4)	0.117

There was no difference in the median number of comorbidities between those who had MRPs and those who did not have; 3 (IQR: 2, 3) vs. 3 (IQR: 2, 4), p = 0.117.

4.7 Multivariate analysis

It was observed that that marital status, estimated glomerular filtration rate ranges, use of ceftriaxone, and use of ceftazidime were significantly associated with occurrence of MRPs due to use of antibiotics. These variables were included in the multivariate logistic regression model (Table 4.16) to assess their joint effect on the occurrence of MRPs due to use of antibiotics. The factors associated with the outcome (MRPs) were selected using backward selection method. This is where all the variables that were significant in the bivariate analysis were included into the multivariate analysis model, then the variables that had the greatest p-value >0.05 were removed one at a time until a parsimonious model was achieved. The only variables that explained the prevalence of MRPs were the use of ceftazidime, and lower estimated glomerular filtration rate.

Table 4.16: Logistic regression model assessing the factors associated with prevalence of MRPs due to antibiotics.

Variable		**Bivariate logistic regression** **OR (95% CI)**	**Multivariate Logistic regression** **OR (95% CI)**
Ceftriaxone	No	Reference	Reference
	Yes	0.32 (0.12, 0.81)	0.52 (0.18, 1.46)
Ceftazidime	No	Reference	Reference
	Yes	7.74 (2.03, 29.5)	**5.62 (1.34, 23.5)**
Estimate Glomerular filtration rate			
CrCL >50		Reference	Reference
CrCL 31-49		3.69 (1.1, 12.4)	2.71 (0.73, 10.1)
CrCL 15-30		3.07 (0.48, 19.8)	3.22 (0.44, 23.5)
CrCL <15		5.46 (1.31, 22.7)	**5.22 (1.18, 23.0)**

The results show that the patients who were using ceftazidime had a higher odds of experiencing MRPs due to antibiotic use compared to those who were using other

antibiotics, **OR: 5.62 (95% CI: 1.34, 23.5) (p=0.001).** Similarly, the patients who had lower estimated glomerular filtration rate (eGFR) <50 mL/min had a higher odds of experiencing MRPs due to use of antibiotics compared to those who had eGFR > 50 mL/min; CrCL 31-49 mL/min vs. CrCL > 50 mL/min: 2.71 (95% CI: 0.73, 10.1), CrCL 15-30 mL/min versus CrCL > 50 mL/min: 3.22 (95% CI: 0.44, 23.5), CrCL <15 mL/min vs. CrCL >50 mL/min: **5.22 (95% CI: 1.18, 23.0) (p=0.016)**. Thus patients who had lower eGFR were more likely to experience MRPs compared to those who had > 50 mL/min of eGFR (table 4.16).

CHAPTER FIVE: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1. Introduction.

This chapter highlights the findings in this study in relation to existing and relevant studies. Study conclusions and recommendations have been drawn from the study findings.

5.2 Discussion.

The proportion of females to males, the unemployed to the employed, married to the unmarried, those who reported never having used alcohol to those who have ever taken alcohol, those who claimed to have never smoked to those who smoke and those with at least primary level of education to those with no education, recruited in the study, were respectively of a higher proportion, reflecting the findings of similar studies carried out in the same setting(17)(32).

While the mean number of medications, age of the participants and the number of comorbidities in our study resembled that of the study by Nyakiba et al.,2015, (17),it contrasted with the study by Njeri et al.,2016, (32). The findings by Njeri et.al.,2016, however, reflects the increased incidence of chronic kidney disease with increasing age, and increased number of comorbidities, and invariably higher number of prescribed medications, in patients with CKD, as reflected in other studies(77)(78).This therefore explains the difference in the mean number of medications, age of participants and number of comorbidities between our study and by Nyakiba et al.,2015 with the study by Njeri etal.,2016,

The prevalence of HIV, anaemia, and cardiovascular conditions in this study were similar to the findings by Njeri et al.,2016, (32) ,but in contrast to those by Nyakiba et al.,2015, (17). The prevalence of TB, Diabetes mellitus, cancers, kidney disease, bacterial pneumonia, bacterial meningitis and hypertension were also low in Nyakiba et al.'s,2015, (17) study in comparison to our study. The reasons for these differences were inexplicable from the scope of our study, however more incident cases and prolonged survival of the existing cases, possibly due to better management of cases over the study periods, can explain the observed higher prevalence in our study.

Cephalosporins were the most widely used antibiotics, a finding reflected by other studies done in the same setting(8)(16)(67). The median number of antibiotics used per participant was 2(1-2) with a range of 0-9. The maximum number of MRPs reported per participant was 4 with 43.6% of the study participants having at least one MRP, and 2.1% of the participants having MRPs experiencing a severe MRP. This prevalence contrasts with findings by other studies, with their reported prevalence ranging from 15.7% (24) to 100% (32), and a closely related study reporting a prevalence of 26.3% attributable to antibiotics use(64). This difference in the prevalence of MRPs is possibly due to the different healthcare practices in the various settings, and the scope of the studies.

Drug-drug interactions and improper drug selection, were the most commonly encountered MRP .This finding correlates with findings by other studies done in the same setting (17)(32) and to the findings of a study by Al Hajje et al., 2012, (24), in a different setting.

The DDI mostly noted mainly involved anticoagulants with other drugs, notably, antibiotics, an observation that has been noted in other studies(79). Antibiotics may increase the anticoagulant effect of enoxaparin or warfarin through cytochrome P450 metabolism pathway where one drug influences the metabolism of the other(80). Rifampin potently induces oxidative enzymes in the cytochrome P-450 pathway affecting the metabolism of other concomitantly administered drugs(81). We noted a potential interaction between warfarin and rifampin in patients who had the two drugs in their regimen.. Also noted were the synergistic interaction effects of antihypertensives with each other and with diuretics which affects blood pressure control and electrolyte balance. There was potential interaction between spironolactone and angiotensin converting enzyme leading to hyperkalemia(82). Other noted interactions involved interference of renal clearance of one drug by the other for example, amoxicillin interference with renal clearance of methotrexate. Concurrent administration of gentamicin and furosemide may result in increased ototoxicity and nephrotoxicity(83). Azole antifungals use with macrolides also noted, with their potential for QTc prolongation. The mechanisms for these interactions have been noted in the review by Madhav M., and Dhara S.,2014(80).

It was also found that improper drug selection was the most commonly encountered MRP , a finding that is closely similar to the findings of 12.2% in a study by Njeri et al.,2016, (32) and 11.5 % in the study by Nyakiba et al.,2015, (17), which were carried out in the same setting. This finding however contrasts the findings in other studies (24)(33)(51)(52)(54) which reported a higher proportion of the IDS ranging from 23% to 54.3%.

The noted IDS situations involved; non-inclusion of a macrolide for the empiric treatment of community acquired pneumonia; use of fluoroquinolone antibiotic for treatment of pneumonia in HIV positive participants (2 cases) before ruling out of tuberculosis infection(84); use of a sulphur-based dermatological cream (silver-sulfadiazine cream) in a participant who had a severe reaction, SJS, to sulphur-based drugs, despite known warning on avoidance of these drugs in known previous severe allergic reaction (85); inappropriate use of both ceftriaxone and tigecycline for a skin infection, and lack of de-escalation despite isolation of S. epidermidis as the infecting organism.

Other cases of IDS involved prescription of both ceftazidime and amoxicillin-clavulanate for a skin infection, instead of either amoxicillin-clavulanate or flucloxacillin or clindamycin or doxycycline; improper use of ceftazidime, nitrofurantoin and ciprofloxacin, and non- de-escalation, despite culture results showing sensitivity to nitrofurantoin, and use of both ceftazidime and amoxicillin-clavulanate plus clindamycin for a soft tissue infection

Also noted was the use of ceftazidime , in the absence of microbiology, culture and sensitivity results, for a skin infection; use of ceftriaxone in a patient with obstructive jaundice, despite reports of possible potential of biliary sludge with ceftriaxone use(86);use of both flucloxacillin and amoxicillin-clavulanate, as empiric therapy for a skin infection, instead of either, and improper use of both meropenem and amoxicillin-clavulanate for a skin infection. All these improper drug use scenarios was based on non-conformity to the KNH guide to empiric antimicrobial therapy, second edition 2018.These improper drug selection scenarios could possibly have been due to multiple teams reviewing a patient and/or delayed transmission of susceptibility study reports to the primary patient-clinical-care-team. However from drug utilization studies by Pradhan

S., et al., 1988(87), we cannot rule out the influence of deficient knowledge about drugs, increased patients to attend to, unconfirmed diagnosis and biased use of certain drugs without scientific evidence, by attending teams, as possible contributors to the observed IDS situations.

Prevalence of over dosage was 12.8% from our study is closely related to the results from the study by Nyakiba et al.(17), done at the same setting, but contrasts the results from other studies(24)(33)(64)(66)(67)(68) which reported higher OD prevalences. But except for the studies by Al-Hajje et al., 201, (24), by Guignard B. and Samer C., 2013, (68) and by Gorgas T. and Solernou P., 2003, (33), the other studies considered MRPs in patients with CKD/renal function compromise, a population which is more prone to drug dosing errors(88). The incidence of drug overdosing in our study mainly involved, lack of appropriate renal dose adjustments of ceftazidime, antimycobacterials, amoxicillin-clavulanate, clarithromycin, and meropenem. The incidence of over dosage could therefore have been relatively low in our study population as it considered drug dosing in patients with and without renal impairment.

Adverse drug reactions had a prevalence of 6.4%, which is similar to findings by Mehta U.et. al., (22), and closely resembles the findings by Abdulla et al.(89), Pirmohamed et al., 1998, (37), and by Nyakiba et al., 2015, (17). It however contrasts findings by Katja et al., 2013, (43), Kiguba et al., 2017, (42), ,Galleli et al.,2002, (41). The diversity in the findings is possibly due to the different scopes and duration of the studies, and the different healthcare practices in the various study sites.

Adverse drug reactions in our study mainly involved; three cases of allergy to cotrimoxazole in newly diagnosed HIV participants put on *Pneumocystis jiroveci* prophylaxis regimen; one case of suspected nephrotoxicity post gentamicin initiation, based on decreasing creatinine clearance on sequential urea, creatinine and electrolyte measurements; and two cases of suspected hepatotoxicity due to antimycobacterials, based on sequential impaired liver function tests, and clinical signs of hepatotoxicity, in participants diagnosed with mycobacterial tuberculosis infection and recently started on the antimycobacterials. Adverse drug reactions due to sulphonamides, aminoglycosides

and antimycobacterials has however been noted in other studies(90)(91)(92), respectively.

Sub therapeutic dosage also comprised 6.4% of the MRPs in our study. This closely relates with the studies by Nyakiba et al.,2015, (17),done in the same setting, which found a prevalence of 7.4%, and by Al-Hajje et al.,2012, which found a prevalence of 10% (24). It however contrasts the findings by Gorgas T and Solernou P., 2003, (33) which reported a prevalence of 22%. The incidences of STD dosage in our study mainly involved; one case each of improper dosing frequency for clindamycin (twice daily instead of thrice or four times daily), cotrimoxazole (once daily instead of thrice or four times daily) and piperacillin-tazobactam (twice daily instead of thrice or four times daily), despite normal renal functions for the participants, and three cases of weight based inappropriate lower doses of Rifampicin (150mg), Isoniazid (75mg), pyrazinamide (400mg), and Ethambutol (275mg) (fixed dose combination(FDC)) tablets of 3 tablets instead of 4 for 57,63 and 68kg weighing participants. These incidences of sub therapeutic dosage was mainly due to inappropriate prescribing regarding the correct dosing for the noted drugs, a factor which can also be attributed to the extent of physician knowledge and workload on certain drug uses(87)

Failure to receive drug, on the other hand, comprised 3.2% of the identified MRPs in our study, a finding that contrasts with the prevalence of 15.5% of FRD, by a study done in the same setting by Njeri et al., 2016, (32). The instances of FRD by our participants involved; lack of intravenous (IV) access line despite the participant being prescribed intravenously administered medications; a non-patent IV access line and in one case, there was a lack of prescribed pyrimethamine as an alternative treatment for Pneumocystis jiroveci, in combination with sulfadiazine, in a participant with known allergy to cotrimoxazole. Lack of drug administration monitoring and prompt provision of alternative therapy, therefore, contributed to the occurrence of this MRP.

Indication without drug accounted for 2.1% of the MRPs in our study. This contrasts with the findings from the same, and other settings, which recorded IWD ranging from 11.2% to 51.3% (17)(21)(32)(68)(75). The instances that we recorded as the reason for the IWD involved lack of Pneumocystis jiroveci prophylaxis in two participants diagnosed with

HIV. The reason for these heterogeneity by the various studies could possibly be due to the scope of the studies, healthcare practices in the various sites, and the number of comorbidities among the study participants.

Finally, *Drug without indication* was the least prevalent MRP in the study. This contrasts with the findings by Nyakiba et al.,2015, (17), McIsaac et al.,2002, (73),and Blix et al.,2004, (21). Importantly, in the studies by Hecker et al.,2003, (18), and by Werner et al.,2011, (74) where unnecessarily prolonged duration constituted 30% and 39%, respectively, of the total days patients were put on antimicrobials. The incidences of DWI in our study involved a case each of prescription of doxycycline and ciprofloxacin without any validated need for antibiotics, a possible lack of request for culture results as scientific evidence for the use of antibiotics, by the patient care team.

The high incidence of MRPs in our study can be attributed to inadequate coverage of the medical wards by clinical pharmacists, whose active involvement in health care systems has been noted to result in decreased incidence of drug related problems through prevention and correction of noted MRPs(93)(94).

In the bivariate analysis, those who were married had a statistically lower prevalence of MRPs compared to those who were single. This effect of marital status has been captured in a study by Kulkarni et al., 2006, (95) which investigated adherence to evidence –based discharge cardiovascular medications which showed that unmarried patients were more likely to discontinue medications unlike married patients. They found out that marital status was a multivariable predictor of good adherence. And in yet another study investigating MRPs in diabetic patients, being of single marital status significantly increased the chances of one having MRPs(96). From this finding we can deduce that spousal support with treatment could have positively influenced the quality of healthcare for our patients and ultimately decreased the incidence of medication related problems.

The prevalence of MRPs significantly increased with a decrease in the rate of estimated glomerular filtration rate**.** Indeed, in the bivariate analysis of association between comorbidities and presence of MRPs due to antibiotics, there was strong evidence that the participants who had kidney disease had a higher prevalence of MRPs compared to those who were not diagnosed with kidney disease. This finding corroborated by multivariate

logistic regression analysis, indicated that patients with lower estimated glomerular rate <50ml/min had a higher odds of experiencing MRPs due to use of antibiotics compared to those who had estimated glomerular filtration rate >50ml/min.

This observation has been highlighted in other studies which indicated increased incidence of dosing errors/MRPs in patients with impaired renal function. In this group of patients, pharmacokinetic and pharmacodynamic alterations in renal drug clearance demands drug dose adjustments based on the level of renal impairment(88)(97). There is usually a correlation between increased comorbidity, increased medication burden, and consequently increased incidences of medication related problems, in these patients(77)(98). There was sufficient evidence to support the difference in the prevalence of MRPs between those who were treated with carbapenem class of antibiotics**,** compared to those who were treated with other classes of antibiotics, a finding that was inexplicable from the scope of our study. However, this may be due to less experience with prescribing of this class of antibiotics by the prescribers and thus the potential for MRPs with its use.

Univariate analysis also indicated that there was statistical evidence that participants who were on ceftriaxone had a lower prevalence of MRPs associated with the use of the antibiotic compared to those who were on other types of antibiotics. This finding conforms with the observations by H. Neu,1990, (99) and by Davis R. and Harriet M.,1994, (100) on the safety profile of cephalosporins, especially third generation cephalosporins. However, although we did not record any fatal outcomes from our study, this finding contradicts the findings of the study by Leone R. et al., 2008, (101) which found ceftriaxone as one of the drugs implicated in the highest number of fatal drug use outcomes in an Italian pharmacovigilance database survey. The low prevalence of MRPs with the use of ceftriaxone is therefore possibly due to its better safety profile and lack of renal dose adjustments in its use.

Participants who were on ceftazidime had a higher prevalence of MRPs associated with the use of the antibiotic compared to those who were on the other types of antibiotics. Participants who were prescribed ceftazidime had higher odds of experiencing MRPs. This was more attributable to lack of renal dosing for ceftazidime for participants with

renal dysfunction, as ceftazidime requires renal dosing in impaired renal function(102), and thus the probable reason for the observed increased incidence of MRPs as compared to ceftriaxone.

And contrasting a systematic review on MRPs and hospitalization by Abdullah A. et al.,2014, (89), the number of drugs prescribed to a participant, number of comorbidities and age did not affect the prevalence of MRPs.

In this study, the preconceived limitations had no effect on the study. None of the recruited participants were unconscious and all data was adequately captured. The clinical features of the adverse drug reactions were clearly distinct from the clinical features of concomitant disease. There were no new prescribers in the medical wards after the launch and dissemination of the KNH guide to empiric antimicrobial therapy, second edition 2018 to all prescribers, and all the participants were randomly selected from the list of admitted patients in the medical wards preventing selection bias.

5.3 Conclusion.

Drug-drug interactions, improper drug selection and over dosage were the most prevalent MRPs associated with antibiotic use in the adult medical wards. Drug-drug interactions mostly involved the use of antibiotics with oral and injectable anticoagulants, and also the use of rifampin in tuberculosis treatment regimens with other drugs. Improper drug selection mostly involved non adherence to the KNH guide to empiric antimicrobial therapy and the type of bacterial infection. While over dosage frequently involved lack of renal dose adjustments, or inappropriate dose adjustments for the level of renal impairment, for antibiotics which are cleared renally.

Significant association between the use of antibiotics and the prevalence of MRPs was observed with the use of ceftazidime and carbapenems**.** There was also a statistically significant association between the prevalence of MRPs and being married and having kidney disease.

Those who were treated with ceftazidime had a higher odds of experiencing MRPs due to antibiotic use compared to those who were treated using other types of antibiotics Participants with lower estimated glomerular filtration rate, eGFR, <15ml/min also had a

higher odds of experiencing MRPs due to use of antibiotics, compared to those who had eGFR >50ml/min.

5.4 Recommendations.

5.4.1 Recommendations for policy and practice

Owing to the prevalence of medication related problems in the use of antibiotics and considering their vital role in the management of bacterial diseases, concerns of increasing resistance, health care costs and morbidity and mortality, there is a need to ensure;

1. There is an active antimicrobial stewardship programs in the hospital to do regular evaluation of antibiotic use and give regular sensitization on their rational use and especially to all new health care staff in clinical areas, including all medical, pharmacy and nursing students.
2. Future revisions of the KNH guide to empiric antimicrobial therapy should reflect the renal (and hepatic) dose adjustments of the most commonly prescribed antibiotics in the set up. All health care teams should be sensitized on the need to cautiously prescribe medications to patients with impaired renal/hepatic function putting into consideration the patient's level of renal or hepatic impairment.
3. Kenyatta National Hospital, and the University Of Nairobi School Of Pharmacy should work on the modalities of ensuring adequate coverage of the clinical areas by pharmacists, especially clinical pharmacists, with the mandate of promoting prudent pharmaceutical care and identifying potential circumstances of improper drug use and putting in place measures to mitigate them.
4. Modalities to amalgamate and implement findings from the various studies done in the hospital should be done to continuously improve on patient treatment outcomes.

5.4.2 Recommendations for research

1. Further research on the risk factors for medication related problems correlated with the use of antibiotics should be carried out in all the clinical sections of the hospital so as to guide in the formulation of hospital-wide strategies to address them.

2. Research on the involvement of clinical pharmacists in pharmaceutical care and assessment of their impact on patient health outcomes in various clinical sections of the hospital should be done.

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APPENDICES

APPENDICES

APPENDIX 1: RECRUITMENT ELIGIBILITY FORM

All study participants enrolled must meet the eligibility criteria outlined in the methodology section and subject to approval by the KNH/ UoN Research and Ethics Committee.

I. Study Information

Study Title: Medication related problems among patients on antibiotics in the medical wards at Kenyatta National Hospital.

Principal investigator: Gilbert Koech Kiprono

Signature……

Date of Screening: ……..

II. Patient Information

Patient code……

Gender: Male □ Female □

III. Inclusion/Exclusion criteria (Tick where appropriate)

Inclusion criteria (**YES** answer to items 1,2 and 6 and either 3 or 4 or 5 confirms eligibility)	**YES**	**NO**
1. Admitted at KNH medical wards.		
2. Age ≥18 years		
3. Prescribed an antibiotic		
4. Has an unmet need for an antibiotic. (Agreement with the responsible physician e.g. lack of co-trimoxazole prophylaxis for PCP in HIV infection where there is no reported allergy to the		

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antibiotic)		
5. Admitted due to an adverse drug reaction or developed an adverse drug reaction likely due to an antibiotic based on medication history.		
6. Voluntarily consents to the study (self /proxy)		
Exclusion criteria **(NO** answer to either of the items 1,2,and 6 or to 3,4 and 5 even if 1,2 and 6 are answered yes)		

APPENDIX 2: CONSENT EXPLANATION AND DECLARATION FORM

Study Title: Medication related problems among patients on antibiotics in the medical wards at Kenyatta National Hospital.

Institution: Department of Pharmaceutics and Pharmacy Practice, School of Pharmacy, University of Nairobi, P.O. Box 30197-00400, Nairobi

Principal Investigator: Dr. Gilbert Koech Kiprono, postgraduate student (Clinical pharmacy) P.o. Box 19676-00202, KNH.

Supervisors:

Dr. Sylvia Opanga, Lecturer, Department of Pharmaceutics and Pharmacy Practice, University of Nairobi.

Dr. Peter Karimi, Lecturer, Department of Pharmaceutics and Pharmacy Practice, University of Nairobi.

I am Dr. Gilbert Koech carrying out a study to partly fulfil requirements for a Masters Degree in Clinical Pharmacy of the University of Nairobi.

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Ethical Approval

Kenyatta National Hospital/University of Nairobi Ethical and Research Committee

What is the purpose of the study?

The study which you are being requested to participate in aims to determine the extent of medication related problems among patients taking antibiotics and admitted in Kenyatta National Hospital medical wards. It further intends to determine any association between medication related problems and patient related risk factors.

Why have I been invited to participate?

You have been approached for consideration as a participant because you are an adult patient who has been prescribed an antibiotic or should be prescribed an antibiotic or because you developed a problem because of using an antibiotic while being treated at KNH or the reason for your admission was because of an adverse reaction possibly due to an antibiotic.

What is expected of me as a participant?

Should you agree to participate in the study, you will be asked to be interviewed using a structured questionnaire to collect socio-demographic data and medical history. This will take less than an hour of your time.

Who will have access to the collected data?

All data collected from you will be coded and entered in a password protected computer without access to the public in order to protect your identity. Only the research investigator will have access to the personal information. However, ethics review committee members may access information if need be to inspect research records. At the end of the study, there will be no way to link your name with the collected data. Any published work, arising from the study, will not bear your name or any other direct identifier

Must I participate? ,

Your participation is completely voluntary. If you decide to participate you are free to withdraw or refuse to answer any questions at any time without jeopardy to your treatment in KNH. You will not be required to give any reason for such withdrawal or refusal.

Are there any benefits of participating?

Immediate benefits to you as a participant is that if any serious MRP is identified, it will be communicated to your physician for review and/or intervention. The information gathered will also give insight into the types of MRPs among patients using antibiotics at KNH. Any observed gaps will inform future treatment services to improve quality of patients care at KNH.

What are the risks associated with my participation?

No risk or harm is anticipated in this study. However, it is possible that you might not be comfortable answering some of the questions in the study tools. All information obtained will be treated in confidence.

What will happen to the study findings?

Study findings will form part of the Master degree in Clinical pharmacy project dissertation. This will further be published in a peer reviewed journal. The findings will also be shared with the University of Nairobi College of Health Sciences administration, KNH administration and in presentations at scientific conferences with the main aim of knowledge sharing for health care improvement.

What do I do in case of a problem?

You are free to raise any concerns about your rights as a participant in this study to my or KNH/UoN Ethics and Research Committee who have approved this study.

CONSENT DECLARATION

Informed Consent by the patient.

I, the undersigned patient, willingly agree to participate in this study. The study purpose, nature, my responsibilities as a study participant and all my questions and concerns have been satisfactorily answered and fully addressed. I understand that I may voluntarily exit the study at any time without any prejudice or penalty to my medical needs at KNH. I understand that the information gathered will be used for the purpose of the study only and none of my personal information or details will be exposed whatsoever, and that I will receive a copy of this signed consent to take away and keep.

Signature……Date……

Informed consent by the patients' proxy

I, the undersigned patient caregiver/relative (proxy) of adult age, has authority to represent the patient and voluntarily, knowingly and competently agree to allow the study personnel to access my patient's medical charts and treatment and answer any questions regarding my patient in regards to this study. I commit not to exert undue influence nor override the patients' wishes to participate in the study. The study purpose, nature, my responsibilities as the patients' caregiver and all my questions have been satisfactorily answered and my concerns fully addressed. I understand that I may voluntarily exit the study on behalf of the patient at any time without any prejudice or penalty to the patient's

medical needs at KNH. I understand that the information gathered will be used for the purpose of the study only and none of my patient's personal information or details will be exposed whatsoever, and that I will receive a copy of this signed consent to take away and keep.

Signature……Date……..

Investigators statement

I, the undersigned, have explained the information in this document to the patient, or their proxy, and have satisfactorily answered all their questions and addressed their concerns. I am satisfied that the participant has understood all aspects of the research as outlined in the consent explanation form.

Name and signature of person obtaining consent.

Name: ……

Signature: …… Date: ……

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In case of any concern you may contact the following;

Principal investigator on email; gillykoech.gk@gmail.com or Tel: 0722757341.

KNH/UoN ERC secretary, Prof. Mark L. Chindia Tel: +254702 72 63 00 Ext; 44355 Email; uonknh.erc@uonbi.ac.ke.

APPENDIX 3: DATA COLLECTION FORM/ QUESTIONAIRE

SECTION A: PATIENT SURVEY

Patient code number……..

I. BIO DATA

What is the patient's bio data? Please fill in these details in the spaces provided

1. Date of birth (DD/MM/YYYY)……..

2. Gender: Male……Female…….

3. Marital status; Single….Married……Widowed…….Separated……..Divorced…….

II. CHIEF COMPLAINT

What is the patient's chief complain? Briefly state in the space below.

……

……

III. HISTORY OF PRESENT ILLNESS

4. What is the patient's history of present illness? Briefly state it in the space below

……

……

……

IV. PAST MEDICAL HISTORY

5. What is the patient's past medical history? Briefly state it in the space below

……

……

……

V. MEDICATION HISTORY

6. What is the patient's medication history? Please conduct a comprehensive medication history and fill in the table below.

Medication & Dose	**Indication**	**Duration** **Start & Stop dates**	**Comments** **(Outcome, Adverse effects)**
Allergies:			
Current drug therapy: Prescription and Non-prescription medicine			
Past medication history(up to 1 month): Prescription and Non-prescription medicines			
Home remedies/Herbal preparations/ Dietary supplements/ Recreational drugs			

VI. FAMILY HISTORY

7. What is the patient's family history? Briefly state in the space below.

.....

.....

.....

VII. SOCIAL HISTORY

8. What is the patient's social history? Please fill in the space below

Occupation:.....

Employed.....Unemployed.....self-employed.....retired.....

Monthly income: <10000..... 10,000- 30,000.....>30,000.....

(Kshs)

Education status: None.....primary.....secondary.....tertiary.....

Alcohol intake: Yes.....No.....

Smoking: Yes.....No.....

If yes for smoking, indicate the calculated number of pack years.....

VIII. REVIEW OF SYSTEMS

9. Is there any complaint from the patient about any of their body system(s) that may be regarded as an adverse effect of the drug (s) being used? Please undertake a comprehensive review of the system and state the nature of involvement.....

.....

.....

IX. MRPs REPORTED BY THE PATIENT

10. Does the patient need more information about his or her medications? Yes ...No

If yes, briefly state their concerns in the space below.

.....

.....

11. Does the patient have trouble using his/her medicines? YES □ NO □

If yes, briefly state their concerns in the space below.

.....

.....

12. Does the patient have trouble understanding or remembering how to take his/her medicine? YES □ NO □

If yes, please list the problems they encounter in the space below

.....

.....

13. Do any patient's medications make him/her feel unwell? YES □ NO □

If yes, please indicate how they feel when the> take medicines in the space below.

.....

.....

14. When patient feels like symptoms are under control, does he/she sometimes stop taking his/her medicine? YES □ NO □

If yes, please indicate which symptoms, when they cease, lead them to stop taking medicine in the space below.

.....

15. Does the patient feel like he/she is taking too many drugs? YES □ NO □ If yes, please indicate their major concerns in the space below.

.....

.....

16. Does the patient feel like the medicine he/she is taking is making him/her feel better? YES □ NO □

If no, please indicate what they feel and which medicine makes them feel that way in the space below.

……
……..

17. Does the cost of patient's medicine make it hard for him/her to take it as prescribed? YES … NO □

If yes please state which medicines they have missed because they find them expensive in the space below.

……
……

18. Whenever the patient has any problem with his/her medication, do they mention it to any healthcare practitioner? YES □ NO □

If yes, briefly state whom they contact and what is done about it in the space below.

……
……..

SECTION B: MEDICATION RECORD AND MEDICATION CHART REVIEW

I. CHIEF COMPLAINT

1. Are there any inconsistencies between the chief complaint by the patient and that in the medical record? YES □ NO □

If yes, briefly clarify it in the space below.

……
……

If yes, what is the chief complaint after agreement with clinician? ……

II. HISTORY OF PRESENT ILLNESS

2. Are there any inconsistencies between the history of present illness by the patient and that in the medical record? YES □ NO

If yes, briefly clarify it in the space below.

.....

.....

If yes, what is the history of present illness after agreement with clinician?

.....

III. PAST MEDICAL HISTORY

3. Are there any inconsistencies between the past medical history by the patient and that in the medical record? YES □ NO □

If yes, briefly clarify it in the space below

.....

.....

If yes, what is the past medical history after agreement with clinician?

.....

IV. MEDICATION HISTORY

4. Are there any inconsistencies between the medication history by the patient and that in the medical record? Yes…..No…..

If yes, briefly clarify in the table below…..

Medication & Dose	Indication	Duration Start & Stop dates	Comments (Outcome,Adverse effects)
Allergies:			
Current drug therapy: Prescription and Non-prescription medicine			
Past medication history(up to 1 month): Prescription and Non-prescription medicines			
Home remedies/Herbal preparations/ Dietary supplements/ Recreational drugs			

V. FAMILY HISTORY

5. Are there any inconsistencies between the family history by the patient and that in the medical record? YES □ NO □

It yes, briefly clarify it in the space below.

.....
.....

If yes, what is the family history after agreement with clinician?

.....
.....

VI. SOCIAL HISTORY.

6. Are there any inconsistencies between the social history by the patient and that in the medical record? Yes……No……

If yes, clarify it in the space below

.....
.....

VII. REVIEW OF SYSTEMS

7. Are there any inconsistencies between the review of systems by the patient and that in the medical record in relation to pharmacotherapy?

Yes……No……

If yes briefly clarify it in the space below

.....
.....

If yes what are the significant findings in the review of systems after agreement with the physician?

VIII. INVESTIGATIONS.

8. Does any laboratory result suggest possible adverse effect of the prescribed antibiotic (s)? Please fill in the relevant results in the table below.

Test/ Investigations	Date(D) carried out, Value (V) and comment(C) as Normal(N) or Abnormal(A)								
	D	V	C	D	V	C	D	V	C
Vitals									
Heart rate									
Blood pressure									
Respiratory rate									
Body Temperature									
Full haemogram									
RBC									
Hb									
MCV									
WBC									
Neutrophils									
Lymphocytes									
Monocytes									
Eosinophils									
Coagulation									
Prothrombin									
APTT									
INR									
UECs									
Na+									
K+									
Mg2+									
Cl-									
Urea									
Cr									
CrCl									
Ca2+									

PO4-									
LFTs									
ALT									
AST									
GGT									
ALP									
Alb									
Tbili									
Ibili									
Dbili									
BGA									
pH									
PO2									
PCO2									
HC03-									
Blood glucose									
RBS									
FBS									
HbA1c									
Others									
LP									
CxR									
ECHO									
ECG									
Urinalysis									
AFB									
MPS									
HIV									
HBV									
HCV									

IX. DIAGNOSIS

9. What is the current provisional or confirmed diagnosis and comorbidities? Briefly state in the space below

Diagnosis	**Indicate whether provisional(P) or confirmed(C)**	**Comment**
Comorbidities		

Total number of comorbidities =

X. MEDICATION RECONCILIATION

10. Please conduct medication reconciliation from the patient interview and medical record review. Please list all prescription and non-prescription medications the patient is currently on specifying the regimen details.

No	**Start Date**	**Stop Date**	**Medicine name**	**Formulation And strength**	**Dose**	**Freq.**	**Route**	**Indication**	**Comment**
Stat/PRN Medications									
1									
2									
3									

4									
Scheduled Medication									
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
			IV Fluids						

Total number of antibiotics, and drugs, the patient is taking =

XI. RESISTANCE REPORTS

Is there any bacterial resistance report? Yes……No….

If yes, state the antibiotic class and type(s) involved……

SECTION C: EVALUATION OF MRPS

I. PREVALENCE OF MRPS

1. Does the patient have any MRPS? Yes……..No……..

If yes please elaborate by filling the sections below. If no the following sections do not apply.

II. CLASSIFICATION

2. Please classify the MRP(s) in the categories outlined below. Please justify by providing a comment. Also note the medicine involved and the therapeutic category to which it belongs

Classification	**Antibiotic Involved**	**Antibiotic class**	**comment**
Adverse drug reaction			
Drug interaction			
Improper drug selection			
Sub therapeutic dosage			
Over dosage			
Failure to receive drug			
Drug without indication			
Indication without drug			

III. MRP SEVERITY

3. What is the severity of the MRP? Is it mild, moderate, severe or fatal? Please justify with a comment.

Severity		**Comment**
Mild		
Moderate		
Severe		
Fatal		

IV. CAUSES OF THE MRP(S)

4. What is/are the cause(s) of the MRP? Please clarify.

Cause	**Due to the antibiotic**	**Comment**
Inappropriate prescribing		
Inappropriate delivery		
Drug/patient idiosyncracy		
Inappropriate behavior by the patient		
Inappropriate Monitoring		

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Ref: KNH-ERC/A/415

16th November 2018

KENYATTA NATIONAL HOSPITAL
APPROVED
16 NOV 2018
KNH/UoN-ERC
P. O. BOX 20723 - 00202 NAIROBI

Dr. Gilbert Kiprono Koech
Reg. No. U56/88154/2016
Dept. of Pharmaceutics and Pharmacy Practice
School of Pharmacy
University of Nairobi

Dear Dr. Koech

RESEARCH PROPOSAL – MEDICATION RELATED PROBLEMS AMONG PATIENTS ON ANTIBIOTICS IN THE MEDICAL WARDS AT KENYATTA NATIONAL HOSPITAL (P627/08/2018)

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 16th November 2018 – 15th November 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**

Protect to discover

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
The Assistant Director, Health Information, KNH
The Dean, School of Pharmacy , UON
The Chair, Dept of Pharmaceutics and Pharmacy Practice,UON
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Ref: KNH/AD-MED/42B/VOL.I/

Date: 21ST November 2018

Dr. Gilbert Kiprono Koech
Department of Pharmaceuticals & Pharmacy Practice
School of Pharmacy
College of Health Sciences
University of Nairobi

RE:APPROVAL TO CONDUCT A STUDY IN MEDICINE DEPARTMENT

Following approval of your study by the KNH/UoN ERC and completion of the KNH study registration certificate, permission is hereby granted to collect data from Medicine Department for your study on ***"Medication related problems among patients on antibiotics in the Medical Wards*** at Kenyatta National Hospital."

Kindly liaise with the Senior Assistant Chief Nurse Medicine Department for facilitation.

Dr K. Ndege

Dr. K.NDEGE
Ag.HOD - MEDICINE

Noted
SACN 22/11/18

Copy to: Senior Assistant Chief Nurse - Medicine

Vision: A world class patient-centered specialized care hospital

ISO 9001: 2015 CERTIFIED