PATTERN OF ANTIMICROBIAL USAGE IN THE ADULT WARDS OF MOI TEACHING AND REFERRAL HOSPITAL, BASED ON THE WORLD HEALTH ORGANIZATION-DERIVED INDICATORS

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DECLARATION

Student's declaration

This dissertation is my original work, being submitted in partial fulfillment of the requirements for the award of Master of Pharmacy in Clinical Pharmacy at Moi University. It has not been submitted for an award of any academic credit in universities or any research institutions elsewhere.

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Declaration by academic supervisors

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DEDICATION

I dedicate this thesis to my family. I thank them for their prayers, understanding, immense support, and continuous encouragement.

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ABSTRACT

Background: Worldwide, infectious diseases are an important cause of morbidity and mortality. The World Health Organization (WHO) estimates that by 2050, these diseases are anticipated to contribute to 13 million deaths worldwide annually, mainly due to antimicrobial resistance. A contributing factor to antimicrobial resistance is the irrational use of antimicrobial agents. To promote the rational use of medicines, specific indicators are used to give an overall pattern of drug usage. The WHO (2012) published a set of key indicators that can rapidly and reproducibly evaluate key antimicrobial usage patterns in a hospital setting. It is important to optimize antimicrobial use to reduce healthcare costs and alleviate rising antimicrobial resistance and associated mortality.

Objective: To assess antimicrobial usage in the adult medical wards of Moi Teaching and Referral Hospital (MTRH) using selected WHO hospital, prescribing, patient care, and supplemental indicators.

Method: This descriptive study was designed using the WHO (2012) prescribed tool to assess 14 specific indicators under the subsections: hospital, prescribing, patient care, and supplemental indicators. Two key informants and their offices provided information: the director of clinical services and the chief pharmacist; and from patient files. Out of 1,138 patients who were eligible (over 18 years and on treatment with an antimicrobial agent), 394 study participants were selected using systematic sampling over 3 months (February to April 2019). Data were entered into Microsoft Excel (MS Office 2010) and analyzed as means, medians, and frequencies (descriptive statistics) as detailed in the WHO tool.

Results: Concerning hospital indicators, there was a lack of standard treatment guidelines for infectious diseases and an up-to-date hospital-specific formulary list. Based on the hospital inventory, only 62.6% of listed antimicrobials were available on day one of the study, while antimicrobials were out of stock for 8.7 days per month. Of the total drug expenditure, 29.4% was spent purchasing antimicrobial agents. Though the WHO recommends 100% use of generic names when prescribing, adherence was only 86.9%. Management of pneumonia complied (98%) with international guidelines. The number of antimicrobials prescribed per patient per hospitalization was between 2 and 3. The average cost, length of therapy, and hospital stay per patient per hospitalization were KShs. 5,727.97/= (USD 52.14); 8.2 days; and 12.2 days respectively. Only 67.3% of antimicrobials prescribed on the treatment records were actually administered. Seventeen (17) out of 83 samples taken for culture had microbial growth.

Conclusion: There were no hospital-specific standard treatment guidelines for infectious diseases, no up-to-date formulary list, and frequent stock-outs of antimicrobial agents. There was high treatment cost and an unacceptable level of prescribed antimicrobial doses not administered to patients. Prescribing of antimicrobials was largely empiric.

Recommendations: A study to determine possible causes and solutions to the gaps identified

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ABBREVIATIONS

ADR	Adverse Drug Reaction
DTC	Drug and Therapeutics Committee
EML	Essential Medicines List
FL	Formulary List
HIV	Human Immunodeficiency Virus
INN	International Nonproprietary Name
IREC	Institutional Review and Ethics Committee
KNH	Kenyatta National Hospital
LMICs	Low and middle-income countries
MRSA	Methicillin-Resistant *Staphylococcus aureus*
MSH	Management Sciences for Health
MTRH	Moi Teaching and Referral Hospital
MU	Moi University
SCAR	Severe Cutaneous Adverse Reactions
SPS	Strengthening Pharmaceutical Systems
STG	Standard Treatment Guidelines
TB	Tuberculosis
USAID	United States Agency for International Development
WHO	World Health Organization

CHAPTER ONE: INTRODUCTION

1.1 Background information

Worldwide, infectious diseases account for some of the most important causes of morbidity and mortality (Jensen & Licht, 2016). Even though antibiotic discovery and use have evolved over the years (Silver, 2011) with the revolutionized treatment of infectious diseases, the World Health Organization estimates that by 2050, these diseases are expected to attribute to 13 million deaths (Gould, 2016) (Jensen & Licht, 2016). This is due primarily to antimicrobial resistance, an emerging global threat difficult for any nation or organization to guard against (WHO, 2014). "No new major class of antibiotics has been discovered since 1987, and too few antibacterial agents have been under development to meet the challenge of multi-drug resistance" (Silver, 2011). Various stakeholders (public-sector partners and pharmaceutical companies) have instituted measures to revitalize the research and development of antibiotics. These measures are estimated to cost $800 million annually (Christine Årdal, 2018). The greatest contributing factor that drives antimicrobial resistance is the inappropriate use of antimicrobial agents, with WHO estimating that approximately 20% – 50% of antimicrobial use is inappropriate (Castro-sánchez et al., 2016) (Gebeyehu et al., 2015). Previously, inappropriate use of antimicrobials was more common in low and middle-income countries (LMICs) with inadequate health care systems. Recently, global patterns in the consumption of antimicrobial agents reveal some convergence between levels of use in LMICs and high-income countries (Gebeyehu et al., 2015) (Klein et al., 2018). Some consequences of inappropriate use of antimicrobials include increased incidence of adverse drug reactions, increased healthcare usage, and cost, and reduced quality of life (Llor & Bjerrum, 2014).

Rational use of drugs entails appropriate administration of medication for the clinical needs of the patient, in appropriate doses for a sufficient time period, and cost-effective to the patients and the community (Quick et al., 2002). This definition is simplified into steps of selecting the right drug at the right dose by the right route at the right time for the right patient (Chaturvedi et al., 2012). Some examples of irrational drug use include poly-pharmacy, incorrect drug dosing or dosing schedule, poor adherence to dosing regimen, use of injections where oral formulations are available, and lack of prescribing guided by standard treatment guidelines, among others (Quick et al., 2002)

Measuring the extent of antimicrobial use in hospitals is important as they reveal trends and benchmarks that may inform interventions for stewardship programs (Fridkin & Srinivasan, 2015). Medicine use indicators are applied for the rapid and consistent evaluation of vital aspects of antimicrobial use. Medicine use indicators are defined as "standardized measurements of various aspects of hospital operations related to pharmaceutical management and use that can be compared to normative ranges to establish the adequacy of performance" (MSH, USAID, 2012). Indicators for investigating antimicrobial use were developed by collaborative efforts and published by the World Health Organization for inpatient use in 2012. These antimicrobial use indicators are 17 in number and have been categorized into hospital (5), prescribing (9), patient care (2), and a supplemental indicator related to drug sensitivity testing (MSH, USAID, 2012). Hospital indicators investigates the existence of standard treatment guidelines and formulary list, stock status, and expenditures on antimicrobial agents. This indicator assesses the hospital's commitment to rational medicine use and quality patient care by providing policies and guidelines adapted to local resistance patterns and antibiotic availability.

Compliance with antibiotic protocols leads to improved clinical outcomes (Howard et al., 2014).

Prescribing indicator measures the average number of antimicrobials prescribed per hospitalization, compliance with a formulary list, the duration of antimicrobial therapy, cost of antimicrobials, duration of treatment, compliance with Standard Treatment Guidelines (STG) for a common infectious disease, use of the generic name. This indicator is a drug-specific indicator that assesses the extent of use of antimicrobials without regard to the disease for which the antimicrobial is prescribed (Pont, 2016).

Patient indicators involve determining the length of hospital stay and the percentage of doses of antimicrobials prescribed that are administered. Optimal therapy with antimicrobial agents is ensured through accurate and timely administration at appropriate frequency intervals. This allows for consistent serum drug levels to be attained, leading to improved patient outcomes (Truong, 2018).

The supplemental indicator measures the extent of use of sensitivity tests to ensure effective antimicrobial therapy through the confirmation of susceptibility to antimicrobial agents as well as enabling detection of resistance (MSH, USAID, 2012) (Jorgensen & Ferraro, 2018).

The World Health Organization (WHO) has postulated that reliable data on medicine use is crucial for assessing the level of access, quality, and cost-effectiveness of care and developing targeted intervention strategies to address problem areas identified. Hence, using the specific indicators for antimicrobial use in hospitals can facilitate identifying common problems occurring from antimicrobial use (Nia et al., 2018).

Although several global point prevalence studies have been done in Kenya, no studies investigating antimicrobial use using the WHO indicators have been done at Moi Teaching and Referral Hospital.

1.2 Statement of the problem

Evidence worldwide indicates that antibiotics are administered ineffectively (in terms of antibiotic timing) or are extended for an inappropriate duration of time (Charani et al., 2017). The standard of care for prescribing and dispensing medicines must be evidence-based. This helps to optimize antimicrobial use to mitigate against the increasing threat of antimicrobial resistance (which is strongly correlated to antimicrobial consumption) (Nordberg, 2013); and to decrease the length of hospital stay, health care costs, morbidity, and mortality (WHO, 2015).

There is inadequate data at the point of care in low-income countries on the use of antimicrobials in humans (WHO, 2015), and it may be challenging for governments to take action based on data from other countries due to differences in the burden of disease (World Health Organization, 2015). Whereas there exist many point prevalence studies on the use of antimicrobial agents in the country, no studies have been done using the WHO indicators investigating antimicrobial use in hospitals. None of the studies on antimicrobial use in the various Moi Teaching and Referral Hospital departments have utilized the antimicrobial use indicators. These offer an in-depth investigation of antimicrobial use at the patient level and may expose crucial problem areas to be addressed to improve patients and community outcomes.

1.3 Justification

Global projections show that by 2050, the health consequences and economic costs of AMR are estimated to be “10 million annual human fatalities and a 2 to 3.5 percent decrease (equivalent to USD 100 trillion) in global Gross Domestic Product” (Rachel,

2017). Therefore, appropriate use of antibiotics must be ensured to optimize healthcare outcomes for all patients. Prudent use of antibiotics can reduce the burden of resistance by reducing the exposure of bacteria to antibiotics. This gives ample time for research and development to yield new antibiotics (Levy et al., 2016).

This study will seek to elucidate the pattern of use of antimicrobial agents in adult medical wards. This is important since understanding the extent of antimicrobial use is a basis for driving action (Rachel, 2017). The results of this study may help in formulating institutional policies on the appropriate use of antimicrobial agents and improve the health outcomes of many Kenyans who undergo medical care every year at MTRH.

1.4 Research question

What is the pattern of antimicrobial usage in the adult wards of Moi Teaching and Referral Hospital based on World Health Organization (WHO) derived indicators?

1.5 Objectives of the study

1.5.1 Main objective

To assess antimicrobial usage in the adult medical wards of Moi Teaching and Referral Hospital (MTRH) using selected WHO indicators.

1.5.2 Specific objectives

(Based on WHO-recommended indicators (MSH, USAID, 2012))

a.) To assess the hospital indicators of the use of antimicrobial agents.

b.) To describe the prescribing indicators of the use of antimicrobial agents.

c.) To evaluate the patient indicators of the use of antimicrobial agents.

d.) To describe the supplemental indicator of the use of antimicrobial agents.

CHAPTER TWO: LITERATURE REVIEW

2.1 Antimicrobial resistance

Antimicrobials are medicines that are used for the treatment and prevention of infections in humans and animals. They include antibacterial, antiviral, antifungal, and antiparasitic agents. Antimicrobial Resistance (AMR) "occurs when bacteria, viruses, fungi, and parasites change over time and no longer respond to medicines making infections harder to treat and increasing the risk of disease spread, severe illness, and death" (WHO, 2018). Antimicrobial resistance (AMR) occurs when microorganisms acquire, express, and transfer resistance genes through natural selection due to antimicrobial selective pressure (Kariuki et al., 2022). Alexander Fleming, the physician-scientist who discovered penicillin in 1945, demonstrated that antibiotics' large-scale and prolonged use could select resistant bacteria. Through laboratory observations, he showed that bacteria sensitive to penicillin could multiply even in increased penicillin concentration. After this, other scientists demonstrated the resistance of tuberculosis bacilli to streptomycin (1947), bacterial resistance to tetracycline and chloramphenicol (the 1960s) (Torres-Caycedo et al., 2019).

Antimicrobial resistance has become widespread globally, and the World Health Organization declared AMR a public health problem in 1999 (Torres-Caycedo et al., 2019). The purpose of carrying out antimicrobial use surveillance and instituting antimicrobial stewardship programs is to prevent antimicrobial resistance. Therefore, establishing patterns and frequencies of resistance globally is pivotal for the formulation of treatment policies geared towards reducing disease burden, morbidity, and mortality (WHO, 2014).

The global report on antimicrobial resistance by the World Health Organization (WHO) details resistance to antibacterial drugs and highlights seven bacteria of

concern internationally. Some examples of implications of these resistant bacteria include the need for more expensive and more toxic second-line drugs to manage the increasing proportions of methicillin-resistant S*taphylococcus aureus*. Countries most affected by a higher burden of disease due to infection with *Shigella* species have gaps in knowledge on resistance patterns despite evidence of resistance to fluoroquinolones from other parts of the world (WHO, 2014).

Compared to other regions, sub-Saharan Africa had the highest mortality rate due to antimicrobial resistance (AMR) in 2019 (23.5 deaths per 100,000). A systematic review of antimicrobial resistance rates in Sub-Saharan Africa (defined as member states from the WHO Africa region) was done using the WHO priority list of pathogens with the addition of *Vibrio cholerae* between 2000 and 2022. Prevalence rates for diarrheagenic *Escherichia coli* were between 15% and 82% reported in 6 countries. In Kenya, the resistance rates of 136 isolates of *E. coli* to the following antibiotics have been reported: ampicillin (83%), tetracycline (83%), chloramphenicol (62%), cotrimoxazole (61%), gentamicin (48%), ciprofloxacin (28%), amoxicillin/clavulanic acid (26%), ceftriaxone (12%), and nalidixic acid (11%). The diarrheal disease caused by Vibrio cholerae causes sporadic cases and epidemics in sub-Saharan African countries. In Kenya, the Inaba and Ogawa serotypes of *V. cholerae* have demonstrated resistance to tetracycline (97%), ampicillin (89%), and nalidixic acid (83%). *Salmonella enterica* serotype Typhi (*S.* Typhi), the bacteria that causes typhoid fever, has exhibited high rates of AMR (more than 70%) in a Kenyan study. The resistance rates of the 144 bacteria isolated to antibiotics were ampicillin (73%), tetracycline (72%), chloramphenicol (72%), and cotrimoxazole (70%). The rates of resistance of *Klebsiella pneumoniae* in sub-Saharan Africa, a pathogen that is the third leading cause of hospital-acquired infections globally, is increasing.

However, the resistance rate could not be quantified since data was scarce (Tadesse et al., 2017).

In East Africa, *Acinetobacter baumanii* has shown a higher prevalence (23%) of carbapenem resistance than other multidrug-resistant (MDR) bacteria. In Kenya, 27 isolates of A. baumanii exhibited resistance to cefepime (100%), meropenem (89%), and levofloxacin (67%). Community and healthcare-associated methicillin-resistant *Staphylococcus aureus* (MRSA) has been reported in 8 sub-Saharan African countries, including Kenya. Due to the lack of surveillance systems in developing countries, data were obtained from single-center studies. The prevalence rates of MRSA ranged from 1.3% to 53.4%; in Kenya, the prevalence was 27.8%. Resistance rates of MRSA for antibiotics were penicillin (92%), cotrimoxazole (57%), tetracycline (33%), and vancomycin (5%). *Pseudomonas aeruginosa* has developed resistance to carbapenems, which are used as a last resort for managing infections. The prevalence rate of carbapenem-resistant *P. aeruginosa* ranges from 6% to 35%, as reported in studies from 6 countries in sub-Saharan Africa. The study concluded that death rates due to AMR were highest in sub-Saharan Africa. Still, effective management of infectious diseases is challenging due to scarce data on antimicrobial use and AMR prevalence compared with developed countries (Kariuki et al., 2022).

The Kenya Working Group for Global Antimicrobial Resistance Partnership conducted a systematic review of 89 articles published between 1974 and 2013 in East African Countries (Kenya, Burundi, Ethiopia, Rwanda, Tanzania, and Uganda) focusing on enteric bacteria causing antimicrobial resistance (AMR). The most commonly studied enteric bacteria were *Salmonella species* (38%), *Shigella species* (38%), *Escherichia coli* (13%), and *Vibrio species* (11%). From the studies, the authors identified possible risk factors that lead to antimicrobial resistance. Factors

contributing to the emergence or persistence of AMR were the transmission of resistant bacteria in the community or hospital, importation of antibiotic-resistant bacteria by humans, limited resources for diagnosis leading to over-prescription of antibiotics in health facilities, and the use of different antibiotics to treat severe infections. Factors contributing to reduced AMR were infrequent antibiotic use, intravenous administration of antibiotics, withdrawal of antibiotics from public use periodically, limited availability, and high cost of antibiotics (Omulo et al., 2015).

Various antimicrobial resistance studies have been conducted at Moi Teaching and Referral Hospital (MTRH). In the pediatrics department, a cross-sectional study was done in the new born unit (NBU) on 141 neonates on antimicrobial therapy for sepsis. *Klebsiella species* (46%) and coagulase-negative *Staphylococcus* (28%) were the most common among the 141 bacterial isolates. *Klebsiella species* was sensitive to amikacin, cefepime, and meropenem; but resistant to ceftriaxone, cefotaxime, gentamycin, and vancomycin. Coagulase-negative *Staphylococcus* was susceptible to amikacin and vancomycin but resistant to cefepime, cefotaxime, penicillin, meropenem, gentamycin, and ceftriaxone (Ateka et al., 2020).

A study was conducted in the surgical departments (general and orthopedic surgery) to describe the antimicrobial susceptibility patterns for bacterial surgical site infections. The causative bacteria for surgical site infections in this study were *Staphylococcus aureus* (40%), *Escherichia coli* (20%), *Acinetobacter baumanii*, *Klebsiella pneumonia*, coagulase-negative *Staphylococcus*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Streptococcus pyogenes*. Fifty-nine percent of the *S. aureus* isolates were methicillin-resistant. All the methicillin-resistant *Staphylococcus aureus* (MRSA) bacteria were sensitive to vancomycin and resistant to azithromycin, cefuroxime, ciprofloxacin, ceftriaxone, and cotrimoxazole. All the gram-negative

bacteria (*E. coli, P. aeruginosa, K. pneumoniae, A. baumanii*) had multidrug resistance patterns, with amikacin and meropenem exhibiting the most favorable sensitivity (Okello, 2018).

A retrospective study was done to describe the antimicrobial susceptibility of bacteria from blood samples of hospitalized patients at the Moi Teaching and Referral Hospital (MTRH) over 12 years. There was 29.9% positive growth from 4046 blood cultures analysed. Most of the samples were from female patients (51.8%) and the new-born unit (62.4%), and the median age was 13 years. The most common bacteria isolated were *Staphylococcus epidermidis* (43%), and *Klebsiella pneumoniae* (23%), *Enterococcus* (9.3%). Both gram-positive and gram-negative organisms reported high bacterial resistance to penicillin and cephalosporins (Oduor et al., 2016).

The prevalence and susceptibility patterns of methicillin-resistant *Staphylococcus aureus* (MRSA) were determined in a cross-sectional study at MTRH between March 2010 and December 2011. Out of 107 *S. aureus* isolates, 39% were MRSA, most from the intensive care unit (ICU) and surgical wards, and a majority of the samples were pus (33%) and tracheal aspirate (17%). The MRSA isolated exhibited moderate susceptibility to linezolid (77%), vancomycin (75%), fusidic acid (67%), high resistance to erythromycin (92%), and tetracycline (92%). The MRSA bacteria isolated also had clindamycin inducible resistance (Akoru et al., 2016).

Analysis of *Klebsiella pneumoniae* isolates from 1356 blood cultures was done retrospectively over 10 years. The highest resistance (over 80%) was reported for cefepime, ceftazidime, ceftriaxone, and gentamycin. The least resistance was reported for meropenem (7%) and amikacin (21%). The authors concluded that the prevalence of multidrug-resistant *Klebsiella pneumoniae* was high at MTRH (Apondi et al., 2016).

A cross-sectional descriptive study was done to describe the antimicrobial susceptibility of bacteria that caused skin and soft tissue infections. Eighty-four bacteria were cultured: 47.6% were *Staphylococcus aureus* (45% were methicillin-resistant), coagulase-negative *Staphylococci*, *Enterococcus species*, and *Streptococcus pyogenes*, among others. The gram-positive bacteria were sensitive to vancomycin and clindamycin, and more than 80% of *S. aureus* were susceptible to ceftazidime and vancomycin. Over 80% of gram-negative bacteria were sensitive to amikacin and meropenem, except Acinetobacter baumanii, which was resistant to all antimicrobials tested (C. Langat & Werunga, 2021).

2.2 Antimicrobial consumption and consequences

There are varying definitions of inappropriate antimicrobial use in different settings. Since no reference standard exists, most evaluations of prescribing practices have adopted expert review to determine appropriate use. However, objective criteria encompassing diagnostic assessment and compliance with literature and treatment guidelines using quality indicators have become a focus point (Spivak et al., 2016).

An internet-based global point prevalence study revealed that the top 3 antibiotics consumed worldwide were penicillin with beta-lactamase inhibitors, third-generation cephalosporins, and fluoroquinolones (Versporten et al., 2018). Only a third of antibiotics were prescribed rationally in a point prevalence study investigating the appropriateness of antimicrobial prescribing and compliance to guidelines at a referral hospital in Kenya. There was a lack of local guidelines for a significant proportion of conditions (Maina et al., 2020). A separate study evaluated self-medication and dispensing practices in Kenya and showed that the most commonly prescribed antibacterial agents were penicillins at 50%, cephalosporins at 12.6%, and fluoroquinolones 11.7% (Mukokinya et al., 2018).

The use of antibiotics inappropriately or for extended durations poses a risk of adverse drug reactions. A retrospective study to assess severe cutaneous adverse reactions (SCARs) due to inappropriate medication use showed that antibiotics, anticonvulsants, and allopurinol accounted for more than 50% of cases. Antibiotics were the largest group involved in unintentional re-challenge (Royer et al., 2018). In the United States, national estimates indicated that 145,490 (13.7%) emergency department visits occurred due to antibiotic adverse events each year. The most frequently implicated classes of antibiotics were oral sulfonamides 23.2%, penicillins 20.8%, and quinolones 15.7% (Geller et al., 2018). Data from a systematic review and meta-analysis showed that the prevalence of *C. difficile* antibiotic-associated diarrhea is 20%. The most important risk factors are advanced age, hospitalization, and exposure to antibiotics, and the most implicated antibiotics are clindamycin, fluoroquinolones, and cephalosporins (Nasiri et al., 2018).

A retrospective study conducted in Kenya using the Pharmacy and Poisons Board database reports between January 2010 and December 2015 showed that 55.3% of antibiotic-associated ADRs were due to cotrimoxazole. Of this, 82.6% were classified as mild-moderate ADRs, leading to drug withdrawal in 79.1% of cases (Njoroge et al., 2018).

2.3 Surveillance of antimicrobial use

Surveillance of antimicrobial use involves monitoring antimicrobial prescribing practices and consumption to reveal strategies needed to inform treatment decisions, evaluate antimicrobial misuse and its public health consequences, and assess the effectiveness of measures instituted to contain antimicrobial resistance (MSH, USAID, 2012).

Data on antimicrobial use is inadequate in low and middle-income countries. National level surveillance of antimicrobial use mainly utilizes sales data to give estimates on antimicrobial consumption. However, this surveillance method does not provide information on how antibiotics are prescribed and used at the patient level (WHO, 2015). Difficulties in obtaining patient-level data have been due to collecting prescribing data from different data sources. Since hospitals have many patients with different illnesses requiring antimicrobial therapy, they provide an excellent setting for studying antibiotic prescribing (MSH, USAID, 2012). Various tools have been developed to carry out surveys or audits of antimicrobial use in the form of medicine use indicators (WHO, 2018).

Efforts by the World Health Organization (WHO) to improve the rational use of medicines globally led to a conference dubbed "Rational use of drugs" in 1985 in Nairobi. One of the resolutions of this conference was to develop a standardized and objective method of measuring prescribing and drug use patterns in health facilities. The drug use indicators were published in 1993 and later revised for use in hospitalized patients. The WHO tool for assessing antimicrobial use in hospitalized patients was developed as a collaboration between the Management Sciences for Health (MSH) and the Strengthening Pharmaceutical Systems (SPS) program sponsored by the United States Agency for International Development (USAID). This tool may be used for conducting antimicrobial use audits, monitoring and evaluating after interventions, and comparing performance among hospitals. The tool provides flexibility for use in the entire hospital or may be adapted to focus on specific departments (MSH, USAID, 2012). The tool has been used in many healthcare settings in different countries. This includes 32 primary health care centers in Pakistan (Sarwar et al., 2018), in 10 selected wards at a tertiary hospital in Pakistan (Atif et al.,

2017), in 1 hospital in India (Nia et al., 2018), in 3 selected wards (medical, surgical, gynecology and obstetrics) in a tertiary hospital in Ethiopia (Demoz et al., 2020), and a tertiary hospital in Eritrea (Amaha et al., 2018).

2.4 WHO antimicrobial use indicators

2.4.1 Hospital indicator

2.4.1.1 Drug and therapeutics committee

The Drug and Therapeutics Committee (DTC) is also referred to as the Medicines and Therapeutics Committee (MTC) or the Pharmacy and Therapeutics Committee (PTC) in different settings. The World Health Organization (WHO) defines a drug and therapeutics committee (DTC) as "the committee that evaluates the clinical use of medicines, develops policies for managing pharmaceutical use and administration, and manages the formulary system" (Serveur, 2004). The DTC comprises a multidisciplinary team of clinicians, pharmacists, nurses, laboratory personnel, and representatives from the hospital administration, such as the administrator and the health records officer. These members are usually the in-charges of their respective departments. The committee chairperson is the medical superintendent or a representative, and the pharmacist in charge is the secretary. The clinicians in the committee include a senior clinical officer and specialists from the internal medicine, surgery, pediatrics, obstetrics, gynecology, and infectious disease departments. The pharmacists in the committee include the pharmacist-in-charge, a clinical pharmacist, or a pharmacologist. A pharmacoepidemiology and pharmacovigilance specialist may also be included if available in the facility (Ministry of Health Kenya, 2020).

The drug and therapeutics committee (DTC) has various functions, some of which require working with other hospital committees, such as the infection prevention and

control committee. The DTC may constitute sub-committees to focus on specific areas of interest or to implement DTC recommendations and activities. Sub-committees include antimicrobial stewardship, safety, pharmacovigilance, supply chain, and logistics. The roles of the DTC involve providing advice to health care providers, developing policies for medicine use (such as the essential medicines list or hospital formulary list), developing standard treatment guidelines, assessment of medicine used to identify problem areas, instituting interventions to improve medicine use, management of adverse drug reactions and medication errors, and dissemination of information on DTC activities and recommendations (Ministry of Health Kenya, 2020) .

Drugs and therapeutics committees (DTC) have existed in the developed world for almost a century. The first described drug and therapeutics committee was formed in a hospital in New York in the 1930s. In the United Kingdom, several hospitals in London had a joint functioning DTC in 1971, a national DTC in Italy started operations in 1977, and Scandinavian countries (Denmark, Norway, Sweden, Finland) since the 1980s. The primary role of the DTCs was formulating restricted drug formularies (Bakke, 1986). In 1977, the World Health Organization (WHO) international expert committee launched the first model list of essential drugs. This essential medicine list (EML) was formulated following a report that reviewed the main drug problems and possible new drug policies in the developing countries, tabled in the World Health Assembly in 1975. The report emphasized the need for an essential medicines list for developing countries due to limited resources, shortage of qualified health care providers, and insufficient drug policies. The list was circulated to the WHO regional offices for adoption or tailoring to the specific health needs of member states (Weltgesundheit, 1978).

An interventional study was conducted in China to investigate whether an optimally functioning DTC would reduce irrational drug use and expenditure and improve the level of drug treatment. Irrational drug use in this 1400-bed tertiary university teaching hospital was classified according to the Pharmaceutical Care Network Europe Drug-Related Problems classification (PCNE-DRP) (version 9.0). There was a 65.98% decrease in irrational drug use between 2016 and 2021, with subsequent improvement in drug treatment levels. Antibiotic utilization rates decreased by 20% overall, 13% in outpatients, and 65% in hospitalized patients over the 5 years. Drug expenses that contributed to total medical income also decreased by 18%. These significant reductions occurred even though the total hospital bed capacity increased from 800 beds in 2016 to 1400 beds in 2021. Conclusions from the study were: DTCs are crucial in safeguarding the rational use of drugs and emphasized the need for professional pharmaceutical technical services (Yang et al., 2022).

In low- and middle-income countries, various stakeholders, such as the management sciences for health (MSH), have partnered with governments to build capacity for drug and therapeutics committee (DTC) related functions and activities. The MSH has worked in African countries, including South Africa, Mozambique, Swaziland, the Democratic Republic of Congo, and Ethiopia. Among these countries, 447 DTCs were formed, and 49 were relaunched. With support from MSH, the Gauteng provincial DTC in South Africa developed guidelines on the operationalization of DTCs at all levels of healthcare. As a result, one of the DTCs in the province used a data collection tool to evaluate drug utilization from the guidelines to assess the consumption of abacavir and cefixime in clinics within the West Rand District. A DTC in Swaziland instituted a quality improvement program to curb antimicrobial resistance. The DTC identified high levels of antimicrobial resistance to ceftriaxone

and vancomycin from culture and sensitivity results of hospitalized patients on antimicrobial therapy. From this finding, the DTC implemented interventions, including developing guidelines on antimicrobial prescription, converting intravenous to oral antibiotics, and a monthly review of antimicrobial susceptibility reports from the laboratory department to inform prescriber antimicrobial selection. In Ethiopia, a drug use evaluation conducted by the DTC of the Dessie Referral Hospital revealed that only 55% of patients received appropriately prescribed ceftriaxone. The interventions by the DTC were a ceftriaxone use policy which outlined the appropriate indications, dosing, duration of use, and completion of medical records indicating the clinical outcomes of ceftriaxone use. A DTC in Waldo General Hospital in Ethiopia conducted a drug utilization review of the combination antimalarial drug artemether-lumefantrine. Though 38% of patients who tested positive for malaria received the drug, the remaining 62% of patients who tested negative for malaria also received the antimalarial drug. These findings led to implementing a sensitization program for all physicians on the national guidelines for managing malaria to improve prescribing practices (Getahun et al., 2015).

The first guideline for establishing the medicine and therapeutics committee (MTC) in Kenya was released in 2015, adapted from the world health organization's (WHO) practical guide on Drugs and Therapeutics Committee developed in 2003. The development of this guideline was anchored in Ministry of Health policies, including the Kenya National Pharmaceutical Policy (KNPP) (2012), Kenya Health Sector Strategic Plan (KHSSP) (2014-2018), and Kenya Health Policy (2014-2030). With the launch of the Kenya Health Strategic Plan (2018-2023), the MTC guidelines of 2015 were reviewed to tailor their establishment in all levels of healthcare within the devolved structure with enhanced roles of technical advice and oversight. The review

culminated in a guideline for the establishment and operationalization of MTCs (2020) anchored in the following policies: KNPP (2012), KHSSP (2018-2023), KHP (2014-2030), and the Health Products and Technologies Supply Chain Strategy (2020-2025). These policies aim to ensure the use of health products and technologies that are safe, appropriate, and cost-effective (Ministry of Health Kenya, 2020).

In Migori County, the hospital MTC implemented interventions to improve the quality of malaria case management, with support from development partners under the United States Agency for International Development (USAID). The MTC benchmarked with a functioning MTC in Kakamega County. These interventions included: regular MTC meetings (monthly), malaria guideline review dissemination, continuing medical education for staff, use of a prescription error book, harmonization of laboratory reporting systems, and development of a hospital formulary. There was an improvement in scores on a clinical checklist from 85% to 96% over 4 months. An 11% decline in clinical improvement scores in the subsequent 6 months was reported due to a prolonged healthcare workers' strike in which all but 3 of the staff trained on malaria case management guidelines participated. The MTC and development partners recommended the incorporation of MTCs into county strategic plans to ensure financial and leadership support for MTC activities (Marube et al., 2017).

In Nyeri County, the MTC implemented many antimicrobial stewardship interventions between 2018 and 2020 for all level 4 and 5 facilities with support from the Medicines, Technologies, and Pharmaceutical Services (MTaPs) program funded by USAID. Sensitization of staff on antimicrobial resistance and rational use of antibiotics was done for clinicians and nurses in the surgery, obstetrics and gynecology, internal medicine, and pediatrics departments. The public was educated

on antimicrobial resistance through presentations and local radio stations. Restriction policies for antibiotics were implemented. The Access, Watch, Reserve (AWaRe) classification of antibiotics was used to implement restriction of prescription of watch and reserve antibiotics by requiring pre-authorization forms duly signed by a medical officer or consultant. A ceftriaxone restriction policy was implemented in the outpatient department except for complicated sexually transmitted infections or pharyngitis not responding to first-line access group antibiotics. Regular follow-up and sensitization were done for clinicians who deviated from this policy. Antibiotic audits in 2019 and 2020 in the outpatient setting assess antibiotic use levels. Clinical pharmacists participated in major ward rounds to advise selecting appropriate antibiotics (Maarifa, 2018).

2.4.1.2 Standard treatment guidelines

Standard treatment guidelines are important as they are used as clinical references for prescribers and contain treatment protocols for the most common infectious diseases encountered in the hospital. The existence and update of these guidelines are an important measure of the hospital's commitment to providing standard patient care and ensuring rational use of drugs (MSH, USAID, 2012).

In 2011, the World Health Organization (WHO) South-East Asia regional office developed detailed steps for developing and implementing the hospital antibiotic policy and standard treatment guidelines (STGs). The report details activities to be executed before the standard treatment guidelines are developed. These are antimicrobial resistance surveillance, antimicrobial consumption, hospital-acquired infections, and hospital or community cumulative antibiogram. This information is then collated into the antibiotic policy, which informs the STG development process and antimicrobial stewardship program. The guidelines should be drafted and

reviewed by a multidisciplinary team of experts. The guidelines should specify the rationale, clinical setting (inpatient, outpatient, critical care), disease-specific, based on local antibiograms, and have evidence-based strength of recommendations (level I to IV). The guideline development process requires the involvement of the clinicians involved in providing care to encourage ownership. The formulated STGs should be validated through an internal peer review process and by experts in the particular specialty who were not part of the STG formulation process. There are many barriers to guideline adherence, including clinicians' lack of awareness, familiarity, agreement, self-efficacy, and motivation. The guidelines may not be convenient to use. Patient preferences, lack of resources, and organizational constraints may hinder the utilization of guidelines (S. E. A. WHO, 2011).

Different organizations in the developed world have programs that create, review and publish guidelines for infectious diseases. The Centers for Disease Control globally, the Society for Healthcare Epidemiology Guidelines of America (SHEA), Infectious Disease Society of America (IDSA) guidelines, and the American Thoracic Society (ATS) in the United States. In Canada, the Public Health Agency of Canada and the Canadian Medical Association (CMA) Infobase contain all the Canadian guideline developers. The British Thoracic Society (BTS) and the British Society for Antimicrobial Chemotherapy (BSAC) are in Britain. The New Zealand Guidelines Group Guideline (NZGG) and National Health and Medical Research Council of Australia in New Zealand and Australia, respectively. The Netherlands had the lowest antibiotic use in Europe, linked to local antibiotic guidelines in 95% of Dutch secondary-level hospitals (Gyssens, 2005).

For many years clinicians in Africa have had to rely on guidelines developed from more developed countries, which do not have the same epidemiological and

antimicrobial susceptibility patterns. In 2018, at a workshop for antimicrobial resistance control by the Africa Centers for Disease Control (CDC) Framework, participants from the African Union (AU) member states agreed that many African countries lacked clinical guidelines to guide the rational use of antimicrobial agents. An exception to this observation was selected diseases such as tuberculosis, human immunodeficiency virus infection, and malaria. The Africa CDC engaged experts from the continent to develop standard treatment guidelines for infectious diseases. The experts retrieved STGs from member states published by their respective Ministry of Health or national government agency responsible for health. Twenty-eight STGs were retrieved from 17 countries and published or revised between 2001 to 2019. For patient populations captured in the guidelines, 20 guidelines covered adult and pediatric patients, 5 guidelines covered only adult patients, and 3 covered only pediatric patients. Many countries had more than one STG; for example, Kenya had the 2009 clinical guidelines for common conditions in hospitals and the 2002 cholera control guidelines. The experts used the IDSA 2018 and WHO 2014 handbooks on clinical guidelines development. The first version of the Africa STG for managing bacterial infections and syndromes was published in 2021. A significant challenge identified during the guideline development process was the lack of data from member states on antimicrobial resistance surveillance (Africa CDC, 2021).

Craig et al. conducted a study to compare standard treatment guidelines for infectious diseases among the member states of the African Union (AU). The guidelines were obtained electronically and through government or public health agency publications on their websites or by communication with the relevant bodies in the country. The STGs were assessed for compliance with the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria. Treatments of interest

were bacterial infections or clinical syndromes with a bacterial cause. The treatments were compared with 3 World Health Organization (WHO) guidelines and across the national guidelines of the AU member states. The 3 WHO guidelines were 2019 WHO Model list of essential medicines (Capello, 2021), 2019 WHO Model list of essential medicines for children (Renevier, 2019), and the Pocket book of hospital care for children (WHO, 2013).

Standard treatment guidelines were available from 20 out of the 35 AU member states. There were 31 guidelines in total, and 7 countries had more than 1 STG. The guidelines were published or reviewed between 2001 and 2018, and 15 (48%) STGs from 10 countries were revised from 2015 onwards. Ten percent of guidelines used the available antimicrobial resistance data, and 32% used data on local disease burden to develop treatment recommendations. None of the countries used the GRADE criteria for guideline development, and the description of guideline development methods was poor. A comparison of the STGs with the WHO guidelines found that only half of the bacterial infections in the STGs were covered in the essential medicines model lists for adults and children, and a third was covered in the pocketbook for hospital care in pediatrics. The authors noted that this discrepancy was likely due to regional and global disease burdens and a lack of capacity for national surveillance. A comparison of the STGs across the member states found variations in the selection and dose of antimicrobial agents and duration of antimicrobial therapy. Few STGs recommended targeted antimicrobial therapy using culture and sensitivity results; and organism-specific treatment. There were fewer variations in the STGs when the antimicrobial therapy for infections was organism-specific. This was demonstrated for the management of acute meningitis caused by *Streptococcus pneumoniae* in pediatric patients, where 5 guidelines had the same recommendations

of monotherapy with either ceftriaxone or benzylpenicillin for 10 to 14 days (Craig et al., 2022).

The WHO suggests that STGs be adapted to specific countries (Joshua et al., 2016). A study in two sub-Saharan African countries investigating the importance of STGs in pediatric practice established that adherence to guidelines and staff capacity building for implementation of guidelines led to better outcomes for hospitalized children in terms of reduced morbidity and mortality (Kruger, 2013).

Treatment guidelines are used to improve antibiotic use. In a point prevalence survey conducted in 14 public hospitals in Kenya, 46.7% of hospitalized patients were on antimicrobial therapy, 0.1% of patients received antimicrobial therapy based on antimicrobial susceptibility test results, and 53.6% received appropriate treatment. Appropriate treatment was defined as antimicrobial prescriptions that complied with standard treatment guidelines, the consensus from experts (where guidelines were unavailable), or antimicrobial susceptibility test results. The only physically available guidelines were the Kenya basic pediatric protocol. The study found that the physical availability of standard treatment guidelines increased the odds of the patients receiving appropriate antimicrobial therapy with an odd ratio of 6.44 [95% CI 4.81-8.64] (Maina et al., 2020).

The available STGs in Kenya by the Ministry of Health are a guide on the management of common illnesses in level 4–6 hospitals (2009) (MOH, 2010), national guidelines for the treatment of sexually transmitted diseases (2018) (NASCOP, 2018), and the basic pediatric protocol (2022) (Mulwa, 2022). There is one local hospital guideline published by a national referral hospital (Kenyatta National Hospital) in collaboration with the University of Nairobi (Maina et al., 2020)

2.4.1.3 Formulary list or essential medicines list

A formulary list is developed because it ensures that medications are selected based on evidence and that selection is unbiased and guides the procurement of antimicrobial agents. One of the essential duties of the drug and therapeutics committee (DTC) is developing and updating the formulary list. The World Health Organization (WHO) defines essential medicines as medicines that meet a population's priority health care needs. These medicines are selected considering the prevalence of disease, relevance to public health, comparative cost-effectiveness, evidence of efficacy, and safety. It is anticipated that these medicines should be available at all times in functional health systems, in the appropriate dosage forms, of good quality, and affordable to individuals and health systems (Capello, 2021). It is challenging for hospital pharmaceutical management systems to be efficient when there are too many medicines. Selecting medicines for the essential or formulary list affects all stages of the drug management cycle: procurement, storage, distribution, and use (prescribing and dispensing). Appropriate selection of medicines for the essential or formulary list may lead to improved quality of patient care and equity in access to essential medicines, and cost containment. Quality of care is enhanced when the medicines listed are derived from evidence-based standard treatment guidelines. Fewer drugs in the essential medicines list (EML) facilitate better training of prescribers to provide better care and alertness on drug-drug interactions and adverse effects compared with many medications. Some policies are required to guide the EML development process. These policies include criteria for selecting medicines for inclusion in the EML, additions or deletions of drugs, level of evidence for recommendation of a drug, and implementation guidelines, among others (Serveur, 2004).

The world health organization (WHO) essential medicines list (EML) was first published in 1977 and has evolved from an experience-based to an evidence-based list. The EMLs have been updated every two years since the first publication. The latest version of the WHO EML for adults (22^{nd} list) was published in 2021. The WHO EML for children was first published in 2007, and the latest version (8^{th} list) was published in 2021. The WHO recommends that the EMLs be updated every 2 years (T. WHO, 2022).

The EML is expected to be tailored to a nation's health needs. A descriptive study compared the EMLs of 137 countries and the 2017 WHO model EML. Out of a total of 195 WHO member states, national EMLs were obtained for 137 (70%), comprising 2068 unique medicines. Except for Sweden and the Syrian Arab Republic, most countries with a low gross domestic product (GDP) had a short national EML. Syrian Arab Republic had a low GDP but a long national EML, while Sweden had a high GDP but a short national EML. Fewer countries listed medicines recently added to the 2017 WHO model list compared to medicines added earlier. None of the countries included all drugs in the WHO EML 2017 list, and velpatasvir, a drug used to manage Hepatitis C, was not included by any of the nations. Eight countries (Kenya, Ethiopia, Pakistan, Moldova, Iran, Syria, Slovakia, and Thailand) had more than 300 medicines from the WHO list on the national list. Kenya, Pakistan, and Moldova recorded medicines with few additions (less than 150 other medicines added to the national EML). In contrast, other countries (Slovakia, Portugal, and Syria) had more than 600 additional medicines in their national EML. Some countries' EMLs (Somalia, Angola, Cambodia, Bosnia and Herzegovina had more than 300 omissions of essential medicines in the WHO list. These differences in additions and omissions of medicines between the national EMLs and WHO model list were driven by a county's healthcare

expenditure. Portugal and Slovakia had a higher healthcare expenditure and many additions, while Angola and Cambodia had lower healthcare expenditure and many omissions. The only drug listed by all countries was Amoxicillin, and 99% of countries included doxycycline, metronidazole, diazepam, short-acting insulin, and salbutamol in their EML. The study examined treatments for diseases (leishmaniasis and trypanosomiasis) that were expected to be listed by a few countries. Findings of the study showed that 8 countries listed 6 medicines for treating trypanosomiasis (benznidazole, eflornithine, melarsoprol, nifurtimox, pentamidine, and suramin sodium), and 96 countries listed 4 medications for treating leishmaniasis (amphotericin B, sodium stibogluconate, paromomycin, and miltefosine). Kenya's EML version 2016 had 74% compatibility with the WHO EML and listed 416 medicines (Persaud et al., 2019).

The formulary list (FL) must be disseminated to prescribers to enhance the rational use of medicines. Lack of awareness or ownership has been cited for low adherence to EML or FL. A cross-sectional descriptive study conducted in a tertiary hospital in North-Central Nigeria assessed the awareness of national EML and hospital FL by 70 medical practitioners (consultants, registrars, and medical officers). The majority (52.9%) of the respondents were in the 31-40 age bracket, 71.4% were male, and were medical officers in service for less than 5 years. Findings for awareness of EML and hospital FL were that 51.4% of respondents were aware of the EML, with 71.7% claiming to have a copy, while 41.4% of respondents were aware of the hospital FL (Hassan et al., 2018).

In low- and middle-income countries, there is a mismatch between drugs listed in the EML and those registered by the regulatory authorities for us in the country. A study in 3 East African countries (Kenya, Uganda, and Tanzania) compared the

antimicrobial products listed on the country's EML and national drug registers. Antimicrobial products on the national EML but not in the drug register were 21%, 27%, and 29% in Kenya, Uganda, and Tanzania, respectively. The drugs not present in the drug register were due to a lack of a manufacturing company to license them for marketing in the country. The antimicrobial products in the drug register but not in the EML were 36%, 47%, and 49% in Kenya, Tanzania, and Uganda, respectively. The authors noted that registered drugs not on the EML might not be on the standard treatment guidelines and, therefore, may be misused (Pollock et al., 2020).

To support antimicrobial stewardship ventures globally, a WHO expert committee created a tool to classify antibiotics into Access, Watch and Reserve categories known as the AWaRe classification. The 2021 update has 254 antibiotics. The tool may be used in tracking antibiotic consumption, setting targets, and evaluating the effects of antimicrobial stewardship activities that aim to enhance the rational use of antibiotics and decrease antimicrobial resistance (Cappello, 2022). Kenya's first essential medicines list was published in 1981, revised in 1993, 2003, 2010, and 2016, and the latest version in 2019. The Kenya EML released in 2019 has also included an AWaRe classification of antibiotics (MOH, 2020a).

2.4.1.4 Availability of antimicrobial agents

The availability of key antimicrobial agents is dependent on the hospital formulary list and greatly influences rational prescribing. The implications of stock-outs of these agents include patients not receiving the appropriate medications or no treatment altogether, which impacts morbidity and mortality (MSH, USAID, 2012). Hindrance to the access of antimicrobial agents has been shown to cause more deaths than antimicrobial resistance (Laxminarayan et al., 2016).

Access to medicines ensures good health outcomes and is an essential component of universal health coverage. A systematic review described the health care system in Kenya and factors affecting access to medicines. The study demonstrated that only about 28% of medicines used in Kenya are manufactured locally. More than 70% of medicines are imported from India (37%), Europe (20%), China (9%), the United States (6%), and South Africa (4%). High reliance on imported medicines causes unavailability and supply chain disruption of pharmaceuticals (Toroitich et al., 2022). Procurement and distribution of pharmaceutical products in public health facilities are mainly done by the Kenya Medical Supplies Authority (KEMSA). Still, for national referral hospitals such as MTRH, procurement is done through independent tenders (Mulaki & Muchiri, 2019).

The Kenya Harmonized Health Facility Assessment (KHFA) report 2018/2019 was developed by the Ministry of Health with support from development partners. The report was prepared by surveying 2,927 (98%) health facilities in Kenya. For all the facilities assessed, the mean availability of essential medicines on the survey day was 44%. Tracer medicines for various diseases were evaluated. The highest availability (70%) was for medicines for managing infectious diseases. The most available tracer medicines nationally were the anthelmintics agents albendazole/mebendazole (85%), and the least available was the antifungal agent fluconazole (45%). Availability of the other antimicrobial agents was cotrimoxazole (78%), ciprofloxacin (75%), amoxicillin (72%), ceftriaxone (66%), and metronidazole (65%) (Bjerrum, 2020). From unpublished data by the Kenya Pharmacy and Poisons Board, more than 50% of the pharmaceutical market share is controlled by anti-infective, cardiovascular, and immunological agents. The authors concluded that lack of essential medicines can lead to underuse, increased medicine out of pocket expenditure of medicines from the

private facilitates, dissatisfaction and distrust of public healthcare services by patients (Toroitich et al., 2022).

In low and middle-income countries, prosperity and economic growth have led to increased use of antimicrobial agents, but there is inequity in improvements of access to antimicrobials. Delays and limited access to antimicrobials have led to more deaths than antimicrobial resistance, particularly in children with pneumonia or febrile illness. Analysis using a Latin Hypercube Sampling model across 101 countries estimated that a mean of 445,000 deaths due to community-acquired pneumonia in children under 5 years could be averted through universal antibiotic provisions. This would represent a 75% reduction in fatalities through access to antibiotics in the pediatric population (Laxminarayan et al., 2016).

Though it is not realistic or necessary to access all antibiotics in all health facilities universally, the World Health Organization (WHO) model list of essential medicines with antibiotics categorized into Access, Watch, and Reserve can facilitate access to key antibiotics. A survey was done on antibiotic availability in 13,561 health facilities in low and middle-income countries. Availability was assessed for 27 antibiotics: 19 access, 7 watch, and 1 unclassified. The overall availability of antibiotics in the health facilities assessed was 49%. Cotrimoxazole, metronidazole, and amoxicillin were available in 90% and 87%, and 84% of health facilities, respectively. Access antibiotics were available in more health facilities than watch antibiotics (Knowles et al., 2020).

2.4.1.5 Stock outs of antimicrobial agents

The average number of days that a set of key antimicrobials is out of stock is used to measure the hospital's capacity to maintain a constant supply of medicines through timely procurement and distribution (MSH, USAID, 2012).

Stock out of antimicrobial agents is a concern globally and locally and prevents timely access to preferred treatment, which causes mortality, especially in low and middle-income countries (Mendelson et al., 2016). Shortages of penicillin and cefazolin have been reported from an analysis of 4-year drug sales data in India. A sharp decline in the number of units sold and sales were observed, which was attributed to price controls by the government (Kakkar et al., 2019). A study done in the United States (US) on the shortage of antibacterial agents between 2001 and 2013 reported a shortage of 148 antibacterial agents over the study period. The antibacterial class with the most reported stock-outs was the cephalosporins, with 27 shortages and 446 months over the 13-year study period. Penicillin/beta-lactam inhibitors had 11 stockouts for 178 months; aminoglycosides had 11 stockouts for 284 months; penicillin had 22 stockouts for 229 months. Some of the antibacterial agents with shortages include cefotetan (5 stockouts for 2141 days), aztreonam (4 stockouts for 1990 days), piperacillin-tazobactam (5 stockouts for 1858 days), and kanamycin (3 shortages for 1682 days). The major reason for stockout in the study was business related to the US economy, affecting manufacturing decisions and leading to supply delays (Quadri et al., 2015).

The cost of antibiotic shortages is estimated at $20-30 million per event due to the selection of more costly substitutes, increased hospital stays, and mortality. In low- and middle-income countries, poor supply of antimicrobials leads to the use of broad-spectrum antimicrobials or suboptimal therapies which contribute to antimicrobial resistance (Baraldi, 2021).

Stock-out of antimicrobials occurred in 95% of health facilities in Australia as reported in a point prevalence survey done in 2017. In the study, stock-outs of piperacillin/tazobactam and gentamicin necessitated substitution with other

antibacterial agents. Shortage of piperacillin/tazobactam resulted in a large increase in more costly options such as intravenous amoxicillin/clavulanate, cefepime, ceftazidime, and intravenous ciprofloxacin. Stock-outs of gentamicin led to increased consumption of amikacin. The total cost increase due to these stock-outs was 22% ($37762) (Khumra et al., 2018).

Possible solutions suggested for addressing antimicrobial stock-outs include improved forecasting of demand to facilitate manufacturers adequately preparing to supply the required antimicrobials, increased buffer stocks for key antimicrobials, enhanced communication from manufacturers on potential shortages, and possible guideline changes to include substitutions in case of unavailability of the preferred antimicrobial agent (Ardal, 2018).

The Kenya health system assessment (2019) reported that health commodity stockouts in the county governments were due to procurement delays, and a lack of timely payment of suppliers (Mulaki & Muchiri, 2019).

2.4.1.6 Expenditure on antimicrobials

Increased consumption of antimicrobial agents may increase the overall health expenditure on medicines. Increases in a hospital's expenditure on antimicrobials may be caused by various factors such as unnecessary use of multiple antimicrobials, inappropriate doses, longer than the recommended duration of treatment, and use of brand names. Determining the hospital's expenditure on antibiotics may inform change and streamline practice to alleviate this cost as the prescriber influences (Royer et al., 2018).

An evaluation of the trends of antibiotic spending was done in public healthcare facilities between 2012 and 2016 in Shandong, China. Data was collected from a

centralized procurement system. There was a 56% increase in antibiotic expenditure from $460 million in 2012 to $717 million in 2016. Expenditure on antibiotics and parenteral formulations increased steadily over the 4 years, and the most procured drug class was the third-generation cephalosporins (Yin et al., 2018).

A study in the United States assessed trends in antibiotic expenditures between 2010 and 2015 from data extracted from a national sales database. There was a 17% decrease in antibiotic spending from $11 billion in 2010 to $9 billion in 2015. Antimicrobial stewardship interventions increased over the study period (Suda et al., 2018).

Prescribing of unwarranted or multiple antimicrobials and use of branded expensive antimicrobials may lead to increased expenditure of antimicrobials relative to total medicines cost within a hospital (MSH, USAID, 2012).

A study was done in a low and middle-income country (Vietnam) to evaluate the expenditure on antimicrobial agents relative to total drug expenditure in 2018 in public healthcare facilities. The data was obtained from pharmaceutical sales data from 52 provincial health departments and 30 public hospitals. There was a 28.7% expenditure on antimicrobial agents relative to hospital medicines costs. The distribution according to antimicrobial class was: antibacterial (28.4%, USD 480 million), antifungals (0.2%, USD 2 million), antiprotozoals and anthelmintics (0.1%, USD 1 million) (Dat et al., 2020).

An ABC (Always, Better, Control)/VEN (Vital, Essential, Non-essential) analysis study was conducted at Dessie Referral Hospital in Ethiopia. The study revealed that expenditure on antibiotics relative to hospital medicines cost 18.3%. one of the most prescribed antibiotics was ceftriaxone, but only 55% of prescriptions with ceftriaxone

were appropriate. This finding led to the formulation of a ceftriaxone use policy to guide rational prescribing of ceftriaxone by clinicians (Getahun et al., 2015).

In Kenya, an ABC/VEN analysis was done in a national teaching and referral hospital (Kenyatta National Hospital) every year between 2013 and 2015. The average annual drug expenditure for antimicrobials was 26.3%. There was a gradual increase in the total drug expenditure and expenditure on antimicrobials every year. The yearly drug expenditure on antimicrobials in 2013, 2014, and 2015 was about 17.3%, 22.7%, and 25.2%, respectively. The authors concluded that since a significant proportion of hospital medicines expenditure was on antibiotics and antineoplastic agents, the drug and therapeutics committees (DTCs) in Kenya should focus on these classes of drugs (Kivoto et al., 2018).

2.4.2 Prescribing indicator

2.4.2.1 Prevalence of antimicrobial use

The extent of using antimicrobial agents in hospitals is vital since observations made over time may detect changes in patterns or trends. The average number of antimicrobials per hospitalization may reveal prescribing patterns about combination therapies, frequency of changes of regimens, and duplication (MSH, USAID, 2012).

A global point prevalence survey conducted in 110 Belgian hospitals assessed antimicrobial use for 28,007 patients with healthcare-associated infections. The percentage of patients on treatment with at least one antimicrobial was 27.1% (95% confidence interval 26.5–27.6%). The most reported healthcare-associated infections were pneumonia, skin and soft tissue infections, and urinary tract infections. Some of the problem areas identified for further investigation and intervention were the high consumption of fluoroquinolones and the high rates of hospital-acquired infections among patients admitted to acute care hospitals in Belgium (Vandael et al., 2020).

A review of antimicrobial use in 20 hospitals for 59,216 patients in Korea revealed a prevalence of 14.1% for all patients and 50.8% for inpatients. The most common illnesses were respiratory tract (29.1%), gastrointestinal (22.4%), and urinary tract infections (13.1%). The most prescribed antibiotic was ceftriaxone, piperacillin/tazobactam, and metronidazole. Concerns from this study were the number of antibiotic prescriptions that were inappropriate (27%) as evaluated by infectious disease experts (Park et al., 2022).

To improve the use of medicines in developing and transitional countries, a systematic review of 900 studies from 104 countries was conducted from 1990 to 2009. The study included public and private health facilities. For the World Health Organization (WHO) regions, the Eastern Mediterranean region had the highest prevalence of antibiotic use at 53.6%, followed by the Western Pacific (50.8%), South East Asia (47.9%), Africa (45.9%), Europe (40.9%), and Latin America (37.0%). The authors observed that the trend in WHO indicators, including antibiotic prevalence, had not changed substantially over 20 years (Holloway et al., 2013).

Many point prevalence surveys on antibiotic use have been conducted in Kenya. The prevalence of antibiotic use was 67% in Jaramogi Oginga Odinga Teaching and Referral Hospital (JOOTRH). The study identified areas of improvement as the high use of empiric antibiotic therapy and the use of antibiotics for prolonged periods for surgical prophylaxis (Okoth et al., 2018). A prevalence survey in a referral hospital in Nakuru revealed that 54.7% of patients were on antibiotics. Some challenges in antimicrobial use identified were a lack of documentation of indication for antibiotic use and high rates of empiric prescribing (Momanyi et al., 2019). A point prevalence survey was conducted on 1,071 hospitalized patients in 3 hospitals in Kenya: the Kenyatta National Hospital (KNH), Moi Teaching and Referral Hospital (MTRH),

and Coast Provincial General Hospital (CPGH). The prevalence of antibiotic use was 43% in KNH, 47% in MTRH, and 52% in CPGH. The average number of patients on antibiotics for all the study sites was 46%. Prevalence of antibiotic use in the medical wards was lower (38%) compared to the critical care (82%) and pediatric wards (59%) (Omulo et al., 2022).

Since the percentage of patients with one or more antibiotics was under determination when formulating this study, this indicator for antimicrobial use was not included in this study.

2.4.2.2 Number of antimicrobials per hospitalization

The WHO recommendation for an average number of antimicrobials prescribed per encounter is 1.6-1.8 for the outpatient setting (WHO, 1993); there are no current existing recommendations for hospitalized patients on antimicrobials (MSH, USAID, 2012).

Single-agent antimicrobial therapy is possible due availability of agents with a broad spectrum of activity that can be utilized in managing mixed infections. The advantages of monotherapy are lower costs and toxicity. Combination therapy offers the benefit of synergistic effects, reduces the development of resistance, and broadens the antimicrobial spectrum of activity, especially for initial empiric treatment. Other additional benefits of specific antibiotics include the anti-inflammatory effect of azithromycin and the antitoxin activity of clindamycin. Using few agents without sufficient antimicrobial coverage to eradicate the causative microorganism may lead to increased mortality. However, unnecessary combination therapy may contribute to the development of antimicrobial resistance. The recommended approach is de-escalation, except in severe infections, and individualized antimicrobial therapy (Pletz et al., 2017).

A cross-sectional study was done in Sudan on prescribing patterns of antimicrobial agents in the adult medical wards of a teaching hospital. The average number of prescribed antimicrobial agents per patient was 2.1. thirty-two percent (32%) of patients were on 1 antimicrobial agent, 41% on 2, and 26% on 3 or more antimicrobials. Some factors associated with multiple antimicrobial agents prescribing that were examined included age, presence or absence of comorbidity, length of hospital stay, and diagnosis. There was a statistically significant association between length of hospital stay, diagnosis, and multiple antimicrobial agents. Patients with more extended hospital stays (more than 6 days) were likely to be treated with 2 or more antimicrobial agents. This was thought to be due to a higher risk of hospital-acquired infections. In terms of diagnosis, patients with infectious diseases or diseases of the gastrointestinal system were more likely to be on 2 or more antimicrobial agents (Abdalla & Yousef, 2019).

A point prevalence survey in 3 hospitals in Kenya showed that 53% of patients were on 1 antibiotic, 40% were on 2 antibiotics, 7% were on 3 antibiotics, and 0.4% were on 4 antibiotics (Omulo et al., 2022).

2.4.2.3 Adherence of antimicrobial prescriptions to hospital formulary list

The level of compliance to the hospital's formulary list reflects the awareness and concurrence of the prescribers with the list, availability of antimicrobials in the hospital, or harmony of use of generic names between the prescribers and dispensers of medications (MSH, USAID, 2012).

Physician experience with a drug, physician preference for other medications, influence by pharmaceutical company sales representatives, and use of studies from unpublished or anecdotal reports are some barriers to optimal formulary decisions (Chase, 2017).

Some reasons for prescriber noncompliance with a formulary list may include lack of awareness, ownership of, or agreement with the list, and listed antimicrobials not available in the hospital. The use of brand names in prescriptions while generic names dispense the medicines is also considered noncompliance with the formulary list in some settings (MSH, USAID, 2012).

2.4.2.4 Cost of prescribed antimicrobials per hospitalization

Access to medicines in many low and middle-income countries is financed through out-of-pocket spending (World Health Organization, 2019). In Kenya, population insurance coverage by the National Hospital Insurance Fund (NHIF) is low at 19%. Insurance coverage is lower in rural areas (14%) compared with urban areas (27%). Thirteen percent (13%) of total health expenditure is due to the cost of medicines, such as out-of-pocket spending (Toroitich et al., 2022). In 20 countries in Africa, 40% of total health expenditure is attributed to out-of-pocket expenses (Adebisi et al., 2022).

Kenya's survey on household income in rural and urban areas was conducted in 2018. The study showed that 50% of Kenyan households earned less than Kenya shillings (KShs.) 10,000/- every month, and 2% of Kenyan households did not earn any income (Mbogo, 2018). A policy brief by the Kenya Ministry of Health on increasing public health investments highlighted some consequences of the high out-of-pocket expenditure on health by Kenyan households. In 2015, 12.7% of sick Kenyans did not seek healthcare due to high costs, and saving depletion due to healthcare expenditure led to the risk of impoverishment for 2.6 million Kenyan households (Njuguna & Wanjala, 2018).

The cost of antimicrobials per hospitalization may be increased due to longer than necessary treatment duration, use of higher than recommended doses, use of multiple

antimicrobial agents, and use of brand-name antimicrobial agents. There are no WHO recommendations for the average cost of antimicrobial per hospitalization (MSH, USAID, 2012).

2.4.2.5 Duration of antimicrobial therapy

The prescriber has a considerable impact on the duration of exposure of antibiotics to the patient. The total duration of therapy is an average of between 7-10 days, with some exceptions. Shorter or more extended treatment periods pose significant risks such as inadequate treatment, causing prolonged suffering due to disease (MSH, USAID, 2012). At the same time, over-treatment introduces a greater risk for adverse drug reactions and increases healthcare costs. Shorter courses are beneficial in managing infections without implications on morbidity and recurrence (Royer et al., 2018).

A commentary in the Canadian Pharmacists Journal by Bradley et al. in 2017 reviewed the practice of counselling patients to "finish the course of antibiotics." The authors discussed the myths that shorter courses of antibiotics are less effective and lead to resistance. The review of studies demonstrated that a shorter duration of antimicrobial therapy was as effective as long treatment durations for common uncomplicated infections with monitoring for clinical improvement. Exceptions included management of otitis media and streptococcal pharyngitis in children under 2 years, chronic or deep-seated infections, and infections in severely immunocompromised patients (Langford & Morris, 2017).

A multicentre randomized controlled trial was conducted to validate the Infectious Diseases Society of America (IDSA)/ American Thoracic Society (ATS) guidelines recommendation for the duration of antimicrobial therapy for community-acquired pneumonia. The results showed that the scores for clinical stability criteria were

similar between the control and intervention groups at 5 days and 10 days (Uranga et al., 2016).

A systematic review of randomized controlled trials compared the longer antimicrobial treatment duration versus less than 7 days of treatment in the management of acute pyelonephritis. The study showed that in patients with acute pyelonephritis, including patients with bacteraemia, microbiological failure, and clinical failure was similar in patients on 7 days course versus a more extended period of 10 to 14 days. The study recommended that patients with urogenital abnormalities may require a longer treatment duration (Eliakim-Raz et al., 2013).

A randomized control trial examined the efficacy of short (5 days) versus standard (10 days) duration of antimicrobial therapy for the management of uncomplicated cellulitis. The study found that levofloxacin given at a dose of 500mg daily had similar efficacy for 5 and 10 days. The clinical outcomes tested were resolved cellulitis at 14 days and lack of relapse at 28 days post study enrolment (Hepburn et al., 2004).

A review of the duration of antibiotic therapy highlighted that antimicrobial resistance results from the overuse of antimicrobial agents, such as unwarranted use of antibiotics without indication. For many infections (except tuberculosis, malaria, *Salmonella typhi*, gonorrhoea, and human immunodeficiency virus (HIV)), antimicrobial resistance is not prevented by completing a course of antibiotics but may be encouraged through a long duration of treatment due to selective drug pressure on bacteria. The duration of antimicrobial therapy should be individualized (Llewelyn et al., 2017).

Biomarkers such as procalcitonin are used to monitor treatment response and guide the stoppage of antibiotics in patients with bacterial respiratory tract infections and

sepsis. To guide antibiotic treatment decisions, a systematic review of 14 randomized controlled trials on procalcitonin algorithms. The study showed lower rates of antibiotic prescriptions and a shorter duration of therapy. Use of procalcitonin levels to guide treatment resulted in reduced exposure to antibiotics without an increase in mortality rate (Schuetz, 2011).

2.4.2.6 Surgical antibiotic prophylaxis

Surgical antibiotic prophylaxis involves the administration of an antibiotic before surgery to prevent the occurrence of surgical site infections. The recommended regimen for antimicrobial prophylaxis is one dose of antibiotic administered at least 1 hour before surgery. Studies have demonstrated that surgical prophylaxis is administered for more than the recommended doses and prolonged durations (MSH, USAID, 2012).

In 3 public hospitals in Jordan, an antimicrobial stewardship committee implemented quality improvement interventions to enhance the rational use of antibiotics for surgical prophylaxis. The interventions, done over 2 years, resulted in an increase in the appropriate choice of antibiotic, the timing of the first dose, and the number of prescribed doses by 86%, 92%, and 88%, respectively. there was a 79% reduction in average cost of antibiotic prophylaxis, and a low incidence of surgical site infections (1.6%) (Getahun et al., 2015).

A cross-sectional study in the surgical, obstetrics, and gynecology wards at Moi Teaching and Referral Hospital (MTRH) described the identity of the common aerobic bacteria that caused surgical site infections and determined their antimicrobial susceptibility. Eighty-four (84) isolates from 63 samples were obtained. Microorganisms cultured from the isolates included *Staphylococcus aureus* (54.7%), *Proteus* species (15.5%), *Pseudomonas* species (12.0%), and *Escherichia coli* (2.3%).

Antibiotics used for post-operative prophylaxis of surgical site infections were ampicillin single agent, ampicillin/cloxacillin fixed-dose combination, amoxicillin/clavulanic acid, gentamicin, and metronidazole. The S. aureus bacteria were sensitive to minocycline (70%), ampicillin (22%), methicillin (20%), chloramphenicol (15%), and cotrimoxazole (15%). Andhoga et al. concluded that a review of prescribing patterns and antibiotic use policies was essential to encourage the appropriate use of antimicrobial agents in the surgical wards (Andhoga et al., 2002).

A previously cited study by Okello et al. in 2018 determined the antimicrobial susceptibility and risk factors associated with surgical site infections in the orthopedic and general surgery wards in MTRH (Okello, 2018). A longitudinal observational study evaluated surgical antibiotic prophylaxis at MTRH, and the outcome of interest was the percentage of patients who received rational (correct time and dose) surgical antibiotic prophylaxis. A total of 446 patients were sampled. For most surgeries, ampicillin was the drug of choice for surgical antibiotic prophylaxis and was administered as a single dose of 2 grams. Post-operative prophylaxis was administered to 30.5% of patients for 3 to 5 days. Surgical site infections were reported in 1.8% of patients. One of the challenges experienced during the study was stockouts of ampicillin (Kakai et al., 2016).

Since this study was focused on adult medical wards and several studies had already been conducted in the surgical wards at MTRH, the indicators of surgical antimicrobial prophylaxis were not studied.

2.4.2.7 Adherence to standard treatment guidelines for antimicrobial treatment of pneumonia

Pneumonia is one of the most common infectious diseases. Comparing the treatment choices for this particular disease presents a uniform manner of assessing the quality of patient care for standard treatment guidelines. However, this is based on the assumption that hospitals already have standard treatments guidelines used by prescribers as a reference point (MSH, USAID, 2012).

An observational study was conducted on 1756 hospitalized patients in 3 emergency care and teaching hospitals in Norway over 5 months. The study investigated the association between national antibiotic guideline compliance and clinical outcomes (length of stay, readmission, and mortality). A higher proportion of patients with lower respiratory tract infections were in the guideline adherent group, while patients with gastrointestinal and urinary tract infections were in the non-guideline adherent group. There was a significant association between guideline adherence, in-hospital mortality, and 30-day mortality. Patients on guideline complaint antibiotic therapy had lower 30-day mortality (odds ratio of 0.48 p=0.003) and lower in-hospital mortality (odds ratio of 0.46 p=0.001). The study concluded that initiating empiric guideline-recommended antibiotics for managing infections led to better clinical outcomes (Wathne et al., 2019).

A systematic review assessed the impact of guideline compliance on antibiotic prescriptions for managing respiratory tract infections. The study compared the effect of guideline implementation on prescribing behaviour of clinicians. Prescriber behaviour improved after the guideline implementation interventions, which led to fewer antibiotic prescriptions and lower treatment-related costs (Oliveira et al., 2020).

In Germany, guideline adherence for management of acute lower respiratory infections was assessed from the health records of 12,880 patients. Fifty-one percent (51%) of antibiotic prescriptions were compliant with guidelines. There was higher guideline compliance in the choice of antibiotics for community-acquired pneumonia (72%) than for cough (27%) and acute bronchitis (22%). Recommendations were made for quality improvement interventions to decrease the gap between antibiotic prescribing practices and guideline recommendations (Kraus et al., 2017).

In Ghana, a cross-sectional survey of 1929 health records of patients with community-acquired pneumonia were done to assess adherence to Ghana's national clinical guidelines and factors affecting adherence to guidelines. There was 32.5% adherence to standard treatment guidelines for the choice of antibiotics for empiric management of pneumonia. Penicillin (73.7%), cephalosporins (12.9%), and macrolides (11.1%) were the major classes of antimicrobials most prescribed. Patients with a prescription of more than one antibiotic, past exposure to antibiotics, duration of primary antibiotic, and documentation of blood pressure, respiratory symptoms, and chest radiograph were less likely to receive guideline adherent antimicrobial therapy. The STG recommended using amoxicillin or erythromycin as first-line agents and cefuroxime or doxycycline as second-line agents for managing community-acquired pneumonia but did not consider options for patients with previous exposure to antibiotics or who may have required more than one antibiotic. Patients who had their clinical and radiographic investigations documented were more likely to receive nonadherent antibiotics because they had severe pneumonia symptoms and had already received amoxicillin/clavulanic acid in the ambulatory care setting (Sefah et al., 2021).

2.4.2.8 Prescribing antimicrobial agents by generic name

The use of International Nonproprietary Names (INN) names versus brand names is beneficial as it reduces confusion, simplifies dispensing, enables ease of selection and purchase of antibiotics as it allows for substitution, and thus facilitates efficiency of hospitals operations. The use of INN means that drugs are prescribed by their active pharmaceutical ingredient. The WHO recommends that 100% of antimicrobial agent prescriptions should be by generic name (MSH, USAID, 2012).

A retrospective chart review of 400 medical records in a hospital in Egypt was conducted to assess whether drugs were prescribed using the generic name. Questionnaires were issued to physicians to determine barriers to using generic names. A total of 2279 drugs were reviewed, and 52.6% were prescribed by generic name. A low proportion of physicians reported having been trained using the INN (38%) or using INN in their practice (48%). Barriers to the use of the generic names by physicians were unfamiliarity with the generic names (79%), lack of sensitization on the use of INN (47%), and concerns about the quality, safety, or efficacy of generic drugs (Mahmoud Soliman et al., 2022).

A study conducted in Tanzania investigated the impact of prescriptions with brand names of medicines. From a retrospective review of 851 prescriptions, 49% of drugs were prescribed using brand names. The pharmacological class of drugs commonly prescribed by generic names was antibiotics (45%) and supplements (21%). The specific drugs include ampiclox (35%), buscopan (9%), and amoxiclav (8%). It was observed that there were more instances of brand name prescribing in the inpatient (59%) than outpatient (39%) departments, probably due to easier prescribing using the electronic medical records systems in the outpatient than manual writing of each antimicrobial agent in the inpatient department (Mwita et al., 2022).

Marketing of medicines by pharmaceutical companies may influence the prescriber to use brand names. In the United States, observations from a study showed that “gifts” from pharmaceutical companies affected prescribers’ behavior. The effect was an increase in prescribing by brand names, higher costs of prescriptions, and more prescriptions per patient (Schwartz & Woloshin, 2019). In the United Kingdom (UK), a review of the ruling by the UK self-regulatory authority showed that 43 pharmaceutical companies had been ruled to have breached regulations in the marketing of their products for off-label use more than once, and 10 companies more than 3 or 4 times over 10 years (Vilhelmsson et al., 2016).

Mixed methods study in Ethiopia was conducted in 3 public and private hospitals in Ethiopia to assess the effect of pharmaceutical marketing strategies (product, promotion, price, and place) on prescriber behavior of 140 physicians. Fifty-six percent (56%) of physicians reported that the marketing strategies affecting their prescribing practices (Hailu et al., 2021). In Kenya, guidelines by the Pharmacy and Poisons Board (PPB) to control the marketing of drugs by pharmaceutical companies exist, but malpractice by sales representatives is still rampant (Toroitich et al., 2022).

A systematic review of the perspectives of pharmacists and physicians on the use of generic drugs revealed that both physicians and pharmacists were aware of the benefits of generic drugs in increasing patients’ access to medicines and reducing costs. However, pharmacists were better informed about bioequivalence than physicians. In developed countries with robust health systems, physicians and pharmacists were more confident in the quality of generic drugs and prescribed them to patients regardless of socioeconomic status. In developing countries with less mature health systems, the participants reported mistrust and a lack of reliable information on the efficacy and quality of generic drugs (Toverud et al., 2015).

2.4.3 Patient indicators

2.4.3.1 Missed doses of antimicrobial agents

The efficacy of antibiotics is dependent on the assumption that doses are administered as prescribed. Factors that may negatively influence the timely administration of doses include stock-outs or errors by healthcare providers (MSH, USAID, 2012).

Lack of adherence to dosing schedules of antibiotics negatively impacts clinical outcomes. A on the effect of missed doses was conducted by the United Kingdom National Patient Safety Agency. Of the 18,527 patients assessed, missed doses caused low to moderate harm in 5405 patients, severe harm in 68 patients, and fatal in 27 patients. Of the 27 patients who died due to missed doses, 33% were due to missed antibiotic doses (National Patient Safety Agency, 2010).

In the United States, a study was conducted on 200 hospitalized patients admitted to a shock trauma intensive care unit to determine the effects of missed antibiotic doses on patient outcomes. The study showed that 184 (92%) patients had missed doses (either off-schedule, completely missed, or both). Of these, 107 (53%) had both off-schedule and completely missed doses of antibiotics. A total of 8167 antibiotic doses were reviewed. There were 2096 (26%) missed doses, 1795 (22%) doses were off schedule, and 301 (4%) doses were missed entirely. For the off-schedule doses, 16% were administered late, while 6% were administered early. For the completely missed doses, 188 (2%) doses were missed for non-valid reasons, and 113 (1%) doses were missed for valid reasons. For the completely missed doses, valid and nonvalid reasons were determined. ‘No reason indicated’ was the most common type of nonvalid reason. Others include: medicine unavailable, previous late dose, inappropriate timing, the patient refused, and the patient was in another department (surgery, radiology, physical therapy) or undergoing a procedure. Valid reasons for missed

antibiotic doses were a change of doctor's orders, the patient held by the doctor, nil per oral (NPO) order, scheduling conflict, hypotension, and high vancomycin trough levels. The number of off-schedule doses increased the length of hospital stay significantly. Still, missed antibiotic doses for valid reasons did not increase the length of hospital stay (Patel et al., 2019).

In a national referral hospital in Uganda, a prospective study was done on 762 hospitalized patients to evaluate missed-dose days of antimicrobial agents. The most frequently prescribed antibiotics were amoxicillin, azithromycin, ceftriaxone, ciprofloxacin, and metronidazole. About 44% of patients who received these antibiotics had at least one missed dose-day of antibiotics. The number of antimicrobial agent doses prescribed that were administered was low. The percentage of antibiotic doses prescribed and administered was 62% for ceftriaxone, 35% for ciprofloxacin, and 27% for metronidazole (Kiguba et al., 2016).

The percentage of patients on antibiotics with at least one missed dose in Uganda (44%) is similar to the results of a multi-site point prevalence survey conducted in Kenya (43%). The highest percentage of missed antibiotic doses was 52% in Coast Provincial General Hospital, 44% in Kenyatta National Hospital, and the lowest in MTRH at 33% (Omulo et al., 2022).

2.4.3.2 Length of hospital stay

Patient indicators for medication use are also determined using the length of hospital stay. Duration of hospital stay or frequent re-admissions may imply disease relapse due to inadequate treatment, treatment failure due to antimicrobial resistance, incorrect diagnosis, or inappropriate treatment. The implications of prolonged hospital stay are increased healthcare costs, increased risk of hospital-acquired infections, and a greater threat of emergence of antimicrobial resistance (MSH, USAID, 2012).

Length of hospital stay may be reduced through the appropriate use of antimicrobial agents. An observational study was conducted in 22 hospitals in the Netherlands on 1890 patients on antibiotics due to bacterial infections. An appropriate switch from intravenous to oral formulations was associated with a shorter length of hospital stay, which was reduced by 4 days (van den Bosch et al., 2016).

Antibiotic authorization may reduce the length of hospital stay. A multisite interventional study in Thailand investigated the impact of pre- and post-authorization for prescribing restricted antimicrobials. The most commonly used antimicrobial agents were meropenem (50%) and piperacillin/tazobactam (36%). The mean length of hospital stay was reduced from 18.9 days in the pre-implementation phase to 15.8 days in the post-implementation phase (Wangchinda et al., 2022).

2.4.4 Supplemental Indicator

This indicator measures the frequency of use of sensitivity tests to ascertain effective antimicrobial treatment. The availability and use of sensitivity tests ensure optimal antimicrobial treatment. Adequate surveillance of antimicrobial susceptibility patterns may inform the hospital's policy change regarding the standard treatment guidelines and formulary list (MSH, USAID, 2012). In low and middle-income countries, diagnostic tests do not always provide value for money since they are more costly than empirical treatment, require qualified staff and infrastructure, and are unreliable (Center for Disease Dynamics, Economics & Policy, 2019).

A previously cited point prevalence study in 3 hospitals in Kenya described the use of culture and sensitivity tests to guide antimicrobial therapy. Two hundred and four (204) patients had a single specified infectious disease diagnosis and received antibiotics. Of these, 27% had culture tests ordered. Moi Teaching and Referral Hospital (MTRH) had the least number of tests ordered (18%), followed by Coast

Provincial General Hospital (CPGH) (26%). Kenyatta National Hospital had the most culture tests requested (34%). The types of samples collected across the 3 hospitals were pus swab (25%), cerebrospinal fluid (25%), blood (15%), urine (11%), stool (9%), and sputum (8%). Data on antimicrobial susceptibility was not collected. The culture tests were ordered for the following most common diagnoses: central nervous system infections (15 tests and 10 results available), pneumonia (15 tests and 11 results), soft tissue infections (14 tests and 11 results), and sepsis (6 tests and 3 results). There was infrequent use of culture and sensitivity tests to guide antimicrobial therapy. One of the suggested barriers to using laboratory tests was the treatment cost, resulting in empiric antibiotics (Omulo et al., 2022).

The WHO antimicrobial use indicators have been summarized in Table 1.

Table 1: Summary of the description of WHO indicators for investigating antimicrobial use in hospitals

	Indicator description	
Hospital indicators	1	Existence of standard treatment guidelines (STGs) for infectious diseases
	2	Existence of an approved hospital formulary list or essential medicines list (EML)
	3	Availability of a set of key antimicrobials in the hospital stores on the day of the study
	4	The average number of days that a set of key antimicrobials is out of stock
	5	Expenditure on antimicrobials as a percentage of total hospital medicine costs
Prescribing indicator	7	The average number of antimicrobials prescribed per hospitalization in which antimicrobials were prescribed
	8	Percentage of antimicrobials prescribed consistent with the hospital formulary list
	9	The average cost of antimicrobials prescribed per hospitalization in which antimicrobials were prescribed
	10	The average duration of prescribed antimicrobial treatment
	13	Percentage of patients with pneumonia who are prescribed antimicrobials in accordance with standard treatment guidelines
	14	Percentage of antimicrobials prescribed by generic name
Patient care indicators	15	Percentage of doses of prescribed antimicrobials actually administered
	16	The average duration of hospital stay of patients who receive antimicrobials
Supplemental indicators	17	Number of antimicrobial drug sensitivity tests reported per hospital admission with curative antimicrobials prescribed

Adapted from "How to investigate antimicrobial use in hospitals"(MSH, USAID, 2012) ****Indicators 6, 11, and 12 were omitted as they were not a part of this study.***

2.5 Knowledge gap on antimicrobial use indicators in MTRH

There exists a paucity of data on antimicrobial use in the adult medical wards of MTRH. Studies on antimicrobials in other departments have touched on causative organisms and susceptibility patterns (Andhoga et al., 2002) (O. Okello et al., 2018) (Ateka et al., 2020) (C. K. Langat, 2018), the prevalence of resistance for specific microorganisms (Apondi et al., 2016), practices of sepsis management (Mathenge & Kussin, 2015), barriers to antimicrobial stewardship programs (Rolfe et al., 2021) and a global point prevalence survey (Maina et al., 2020). None of these studies have used the specific indicators by the World Health Organization (MSH, USAID, 2012), which takes an in-depth look at antimicrobial use to identify specific problem areas that will need improvement for better patient and community outcomes.

CHAPTER THREE: METHODOLOGY

3.1 Study design

This was an observational study carried out over 3 months (February 2019 - April 2019).

3.2 Study site

The study was conducted at Moi Teaching and Referral Hospital (MTRH), a teaching hospital for Moi University School of Medicine. Situated in Eldoret, Uasin Gishu County, MTRH is a referral hospital and serves 22 counties in the former north Rift Valley, Western and Nyanza provinces. The catchment population is 20 million, roughly 40% of the Kenyan population.

The MTRH adult medical ward has a total bed capacity of 183; 96 in the male ward and 87 in the female ward. Each ward, male and female, is organized into 4 firms. Each firm is under the supervision of a consultant physician and has designated teams comprising registrars, medical officers, pharmacists, clinical officers, nurses, nutritionists, counselors, and physiotherapists. However, the multidisciplinary teams were not always complete since pharmacists or clinical pharmacists were not enough to cover all wards.

3.3 Study population

Hospital indicators:

Hospital administrators and managers

Prescribing, patient care, and supplemental indicators:

Adult patients who were admitted to the adult medical wards and on antimicrobial therapy.

3.4 Eligibility criteria

3.4.1 Inclusion criteria

Inclusion criteria for hospital indicators:

As per the recommendations of the WHO (MSH, USAID, 2012), the participants required to provide information for the hospital indicators were:

- Hospital director of clinical services (who was also the chair of the drug and therapeutics committee)
- Chief pharmacist with assistance from the pharmacy administrator and the hospital stores manager

Inclusion criteria for prescribing, patient care, and supplemental indicators:

- Adult patients (over the age of 18 years), admitted to the adult medical wards.
- On antimicrobial therapy.
- Consented to participate in the study.

3.4.2 Exclusion criteria:

Exclusion criteria for prescribing, patient care, and supplemental indicators:

Patients on management with antiretroviral and/or antituberculosis therapy only without other antimicrobial agents.

These were excluded because Kenya has a TB and HIV program funded by the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) through stakeholders such as the Kenya Ministry of Health that spearhead efforts towards strengthening HIV and TB prevention and control. This program's workload and commodity management are run separately, with monthly reports on patients served and medicine consumption surrendered to the partners through the ministry of health. Patients with HIV or TB that were also on antimicrobial therapy were included in the study.

3.5 Sampling and procedures

3.5.1 Sample size determination

The sample size was determined to obtain the required number of study participants to assess the prescribing, patient care, and supplemental indicators.

The sample size was calculated using the Fischer formula stated below (Fisher et al., 1991):

$$\mathbf{n} = \frac{\mathbf{Z}_{\frac{\alpha}{2}}^{2} \ \mathbf{x}\ \mathbf{P}(1-\mathbf{P})}{\mathbf{d}^{2}}$$

Where,

n: minimum sample size required for a large population (≥ 10,000)

$Z_{\alpha/2}$: critical value for a 95% confidence interval (=1.96 from Z- table)

P: proportion of patients on antimicrobials as shown in previous studies 55.4% (Momanyi et al., 2019)

d: margin of error (5%)

Therefore, estimated minimum sample size was:

$$n = \frac{(1.96)^2 \times 0.554(1-0.554)}{(0.05)^2} = 379$$

Since the study population was less than 10,000 (6570 admissions in the adult medical wards in 2018) the sample size was reduced using the following formula.

$$\text{Corrected sample size} = \frac{\mathbf{n \times N}}{\mathbf{n+N}}$$

n: source population

N: estimated sample size for N≥ 10,000 population

According to the MTRH health records department (2019), an average of 18 patients was admitted daily in the adult medical wards, making up 6570 admissions per year. Then the corrected sample size =

$$\frac{6570 \times 379}{6570 + 379} = 358$$

The corrected sample size with a 10% contingency for incomplete medical records of the patient and non-response was 394 patients.

3.5.2 Sampling technique:

Prescribing, patient care, and supplemental indicators

The sampling technique was applied to obtain the 394 study participants required. The study participants were sampled from the male and female wards. Systematic sampling was used to recruit 6 patients (3 males and 3 females) per day for 5 days per week over 3 months. There is one male and one female ward. For ease of management, patients in each male and female ward are further subdivided into four groups designated as firms, such that there are eight firms within these two wards. Each firm has a full health care team overseeing it. One male and one female firm admits each day (24-hours) that is two firms per day

The admitting firms' admissions book and treatment sheets (male and female) were used to identify the total number of eligible study participants per firm for that day. The total number of study participants was used to calculate the nth value for each firm (for example, for 18 study participants, this was divided by 3 to get an nth value of 6. Every 6^{th} patient on that day in that firm would be selected to participate in the study. Informed consent was then obtained using the informed consent form in

Appendix F. All the patients selected granted informed consent to participate in the study.

3.6 Data management

3.6.1 Data collection methods

The data was collected by the researcher and a trained research assistant. Data on hospital indicators was collected on the forms as Appendix A (Instrument 1: Basic information), Appendix B (Instrument 2: Availability of a set of key antimicrobials and time out of stock), Appendix C (Instrument 3: Cumulative purchase of antimicrobials) and Appendix D (Instrument 4: Antimicrobials purchased). This data was collected from members of the hospital's administration (the hospital director and chief pharmacist) (for determination of the existence of standard treatment guideline and formulary list) and electronic inventory management data from the hospital stores (for indicators on availability, stock outs and expenditure of antimicrobial agents). Data for indicators on STGs, formulary list and availability of antimicrobials were collected at the study's beginning (Day 1). Indicators on stock outs and expenditure on antimicrobials were collected at the end of each month for the study period. For indicators on availability, days out of stock and expenditure on antimicrobials, data collected was for the hospital stores and not the specific pharmacy that supplies the adult medical wards. This is because a weekly availability list for the hospital stores was routinely provided to the pharmacists on ward rounds by the chief pharmacist. Therefore, the patients in the ward had access to all drugs on this list and were not restricted to only the drugs available in the adult medical wards' pharmacy. Additional questions on Appendix A were answered for indicators on expenditure on antimicrobials (questions 12 and 13) and drug sensitivity tests reported per hospitalization (question 11).

For the prescribing, patient care, and supplemental indicators, information was collected for the 394 study participants sampled from the adult medical wards who had given informed consent using the form in Appendix F. The demographic characteristics (age and gender) were noted. The information for indicators on number of antimicrobials per hospitalization, adherence to formulary list, cost of antimicrobials, duration of antimicrobial therapy, adherence to pneumonia guidelines, generic name prescribing, missed doses, length of hospital stay, and utilization of antimicrobial sensitivity were collected in Appendix E (Instrument 5: Form to record antimicrobial treatments). Follow-up for each study participant was done up to discharge or 30 days, whichever was earlier.

More information on the data collection method applied for this study is in Appendix G [section A (on page 62) for hospital indicators and section B (on page 63) for prescribing, patient care, and supplemental indicators].

3.6.2 Data entry

Data collected on the prescribed forms (Appendix A, B, C, D, and E) were checked for completeness and correctness before data entry was done. Data were entered into Microsoft Excel (MS Office 2010) by the researcher.

3.6.3 Data protection and security

Hard copies of collected raw data were kept under lock and key and will be saved for a minimum of 5 years. All the electronic data was password-protected, only accessible to the researcher. For confidentiality purposes, all participants' records were de-identified. Data was also backed up in two separate storage devices to safeguard against loss.

3.6.4 Data analysis

The study variables were analyzed by descriptive statistics using Microsoft Excel (2010). Data for various indicators were summarized as mean, medians, percentages, frequency distributions, guided by formulas provided in the WHO data collecting tool. The formulas were obtained from *"How to investigate antimicrobial use in hospitals"* (MSH, USAID, 2012) (Table 2).

Table 2: Determination of selected indicators for antimicrobial use

	Indicator description	Determination
Hospital indicators		
1	Existence of standard treatment guidelines (STGs) for infectious diseases	Recorded the existence STG and date last revised
2	Existence of an approved hospital formulary list or essential medicines list (EML)	Recorded the existence of EML, date last revised, and number of generic antimicrobials (counted as the active antimicrobial ingredient and not formulations)
3	Availability of a set of key antimicrobials in the hospital stores on the day of the study	$\frac{\text{Number of antimicrobials in stock}}{\text{Number of antimicrobials that should have been in stock}} \times 100$
4	The average number of days that a set of key antimicrobials is out of stock	$\frac{\text{Sum of the number of days that each antimicrobial is out of stock}}{\text{Number of antimicrobials in review}}$
5	Expenditure on antimicrobials as a percentage of total hospital medicine costs	$\frac{\text{Total cost of all antimicrobials purchased}}{\text{Total cost of all medicines purchased}} \times 100$
Prescribing indicators		
7	The average number of antimicrobials prescribed per hospitalization in which antimicrobials were prescribed	$\frac{\text{Total number of antimicrobials prescribed for all study participants}}{\text{Total number of study participants}}$
8	Percentage of antimicrobials prescribed consistent with the hospital formulary list/EML	$\frac{\text{Number of antimicrobials prescribed that are on the EML}}{\text{Total number of antimicrobials prescribed}} \times 100$
9	The average cost of antimicrobials prescribed per hospitalization in which antimicrobials were prescribed	$\frac{\text{Total cost of all antimicrobials prescribed}}{\text{Total number of study participants}}$

10	The average duration of prescribed antimicrobial treatment	$\frac{\text{Total number of days on antimicrobial treatment}}{\text{Total number of study participants}}$
13	Percentage of patients with pneumonia who are prescribed antimicrobials in accordance with standard treatment guidelines	$\frac{\text{Number of study participants with pneumonia treated only with antimicrobial per STG}}{\text{Total number of study participants with pneumonia}} \times 100$
14	Percentage of antimicrobials prescribed by generic name	$\frac{\text{Number of antimicrobials prescribed by generic name}}{\text{Total number of antimicrobials prescribed}} \times 100$
Patient care indicators		
15	Percentage of doses of prescribed antimicrobials actually administered	$\frac{\text{Total number of doses of antimicrobials administered}}{\text{Total number of doses of antimicrobials prescribed}} \times 100$
16	The average duration of hospital stay of patients who receive antimicrobials	$\frac{\text{Total number of days of all hospitalizations for study participants}}{\text{Total number of study participants}}$
Supplemental indicators		
17	Percentage of antimicrobial drug sensitivity tests reported per hospital admission with curative antimicrobials prescribed	$\frac{\text{Total number of study participants with a sensitivity test performed}}{\text{Total number of study participants}} \times 100$

3.7 Ethical approval and consideration

The study commenced after obtaining approval from the MU (Moi University)/MTRH Institutional Review and Ethics Committee (IREC) Formal Approval Number FAN: IREC3189. Permission was sought from the hospital administration to carry out the research (MTRH Ref: ELD/MTRH/R&P/10/2/V.2/2010)

Confidentiality was maintained during the study. Signed and dated informed consent forms (Appendix F) were obtained from the study participants before participating in the study. For the study participants, unique numerical identifiers were used throughout the study to safeguard their identity. Data collection materials were kept

under lock and key for hard copy materials and password protection for the soft copy materials.

3.8 Recruitment schema for the study

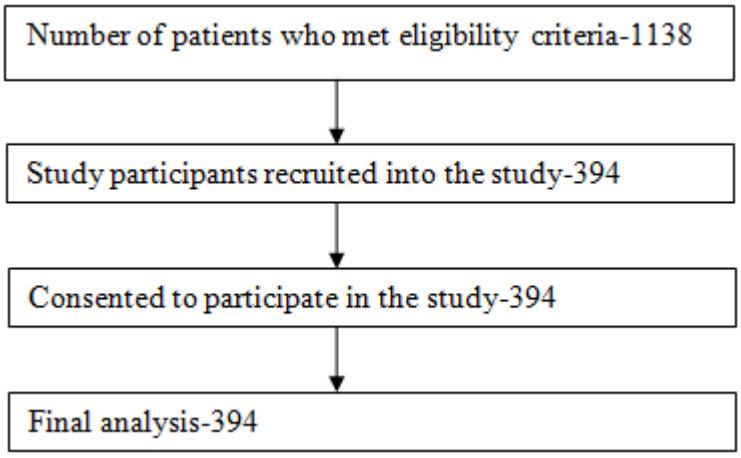

Figure 1: Recruitment schema

CHAPTER FOUR: RESULTS

4.2 Description of hospital indicators

4.2.1 Indicator 1. Existence of standard treatment guidelines for infectious diseases

The hospital did not have local hospital-designed standard treatment guidelines (STGs) for the adult medical wards. On the date of data collection (4th February 2019), the hospital had a Drugs and Therapeutics Committee (DTC) whose last meeting was in June of 2018 (no record of a meeting in the 8 months before the start of this study).

4.2.2 Indicator 2. Existence of an approved hospital formulary list or EML

The hospital had a formulary list (FL) version 2010 that contained 40 antimicrobial agents (counted as the active antimicrobial ingredient and not as varied formulations of a single agent), all of which were identified by generic name. The hospital was not actively using the old formulary list. Instead, it used the Kenya Essential Medicines List (KEML) version 2016, the most recent version of the national formulary list as of the time of the study (February-April 2019). The KEML (2016) contained 45 antimicrobial agents (counted as the active antimicrobial ingredient and not formulations). All antimicrobials on the KEML were identified by generic name.

4.2.3 Indicator 3. Availability of a set of key antimicrobials in the hospital stores on the day of the study

The data for this indicator was collected only on one day, day one of the study (3rd February 2020), as guided by the WHO tool (MSH, USAID, 2012). The antimicrobials were counted based on formulations (antimicrobial name, form, and strength) and not active antimicrobial ingredients. A set of key antimicrobials was defined as those approved by the hospital administration for use in the hospital (those listed in the inventory management software used for supply chain management of medicines in the hospital). In this study, this list served as the hospital-adapted essential list of drugs and formulations and as the denominator for a number of the subsequent indicators in place of the hospital formulary list.

An assessment of the availability list on this single day confirmed that 42 antimicrobial formulations were in stock versus 67 (62.6%) antimicrobial formulations that should have been available. Therefore, the availability of a set of key antimicrobials in hospital stores at the beginning of the study was 62.6%.

The distribution of major classes of antimicrobials available on the day of study is shown in Figure 2.

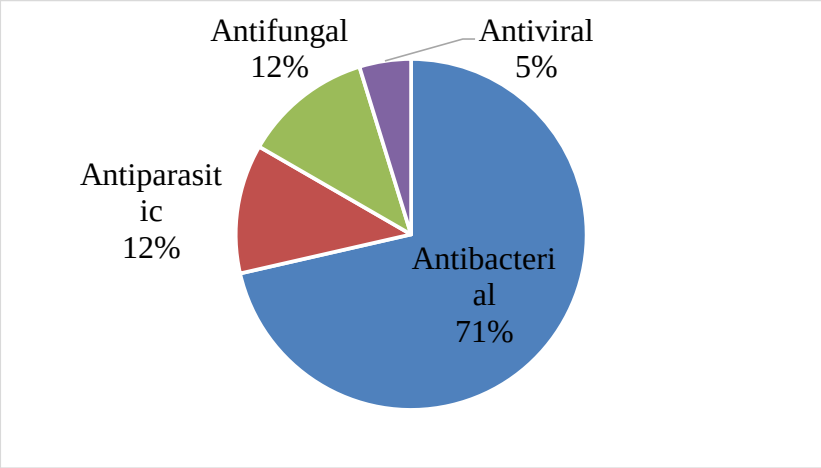

Figure 2: Antimicrobial formulations in the major antimicrobial classes available at the hospital stores at the beginning of the study

See Table H1 in Appendix (page 66) for a more comprehensive table of availability of antimicrobials in the hospital stores on the day of the study

4.2.4 Indicator 4. The average number of days that a set of key antimicrobials is out of stock

The days out of stock were assessed for the 67 antimicrobial formulations (antimicrobial name, form, and strength and not as the active antimicrobial ingredient) at the hospital stores over the three months of the study, as derived from the hospital records. The data was collected at the end of the study period. As shown in Table 3, the total number of days each antimicrobial formulation was out of stock was 1745 days. The average number of days out of stock over the three-month study period was 26.04 days, translating to 8.68 days per month. This means that at least one antimicrobial formulation was out of stock for eight days in a month. Notably, the antiviral agents were out of stock more than two-thirds of the month on average. Of the 67 antimicrobial formulations reviewed, 36 (53.7%) were at least out of stock on one or more days out of stock, while 31 (46.3%) had no days out of stock.

Table 3: Days out of stock for antimicrobial agents at the hospital stores over 3 months

No.	Antimicrobial class	Number of antimicrobial agents in their dosage forms (n, %)	Total days o/s over 3 months	Average days o/s per month
1	Antibacterials	46 (68.66%)	1294	9.38
2	Antiparasitics	8 (11.94%)	56	2.33
3	Antifungals	9 (13.43%)	144	5.33
4	Antivirals	4 (5.97%)	251	20.92
	TOTAL	**67**	***1745***	***8.68***

See Table H2 in Appendix (page 67) for a more comprehensive table of days out of stock for specific antimicrobial formulations.

4.2.5 Indicator 5. Expenditure on antimicrobials as a percentage of total hospital medicine costs

In the previous financial year (2017/2018), the hospital had a budget of KSh. 424,820,680.00 /= for medicines, and the total hospital expenditure on medicines was KSh. 428,460,201.85/=. Therefore, the over-expenditure on medicines was KSh. 3,639,521.85/=. For the study period (February to April 2019), an assessment of the electronic records at the hospital stores showed that the total cost of all medicines purchased was KSh 127,611,477.48/=. From the purchase data reviewed, the total cost of antimicrobials purchased was KSh 37,543,143.10/= (Table 4), making up 29.42% of expenditure on antimicrobials as a percentage of total hospital medicine costs. Almost the entire expenditure on antimicrobials (94.86%) was used to procure drugs against bacteria than drugs against other groups of anti-infective agents.

Table 4: Expenditure on antimicrobials at the hospital stores for the study period

No.	Antimicrobial class	Number of antimicrobial agents (n, %)	The total cost of antimicrobial (KSh.)	Percentage cost of total
1	Antibacterials	25 (73.5%)	35,615,498.60/=	94.86%
2	Antiparasitics	4 (11.8%)	148,639.50/=	0.40%
3	Antifungals	4 (11.8%)	1,493,980.00/=	3.98%
4	Antivirals	1 (2.9%)	285,025.00/=	0.76%
	TOTAL	**34 (100%)**	**37,543,143.10/=**	**100%**

See Table H3 in Appendix (page 68) for a more comprehensive table on expenditures for specific antimicrobial formulations.

4.2.6 Summary of hospital indicators

Table 5: Hospital indicators summary findings and WHO recommendations

Indicator No	Indicator description	Findings	WHO recommendation
1	Existence of standard treatment guidelines (STGs) for infectious diseases	Not available	Should be available
2	Existence of an approved hospital formulary list or essential medicines list (EML)	Yes (Kenya Essential Medicines List 2016)	Yes
3	Availability of a set of key antimicrobials in the hospital stores on the day of the study	62.6%	100%
4	The average number of days that a set of key antimicrobials is out of stock	8.68 days per month	0
5	Expenditure on antimicrobials as a percentage of total hospital medicine costs	29.42%	20-40%

Abbreviations: DTC-Drug and Therapeutics Committee, STG-Standard Treatment Guidelines

4.3 Description of Prescribing Indicators

4.3.1 Recruitment and demographic characteristics of study participants

The study was carried out among 394 study participants at the adult medical wards of Moi Teaching and Referral Hospital (MTRH), as shown in Figure 1. There were an equal number of males and females (197, 50%). The mean age of the study participants was 45.93 years. In this study population, 55 (13.96%) had HIV infection without TB, 15 (3.81%) had TB infection without HIV and 15 (3.81%) had HIV/TB co-infection.

4.3.2 Indicator 7. The average number of antimicrobials prescribed per hospitalization

This indicator measured the extent of antimicrobial use in adult medical wards. Among the 394 study participants, a total of 894 antimicrobial agents were prescribed. This yielded an average number of antimicrobials prescribed per hospitalization of 2.3, meaning study participants were prescribed between 2-3 antimicrobials per admission.

The study participant prescribed the highest number of antimicrobial agents had 8 antimicrobial agents (Figure 2) during a hospital stay of 21 days. This study participant was being treated for hypertension and diabetes. The antimicrobial agents were initially prescribed empirically until a diagnosis of urinary tract infection was obtained from urine culture and sensitivity results. The 8 antimicrobial agents administered in this study participant were: ceftriaxone (from 9/3/2019 for 2 days), cefepime (from 10/3/2019 for 5 days), levofloxacin (from10/3/2019 for 2 days), piperacillin/tazobactam (from 14/3/2019 for 2 days), linezolid (from 14/3/2019 for 12 days), metronidazole (from 23/3/2019 for 12 days), meropenem (from 23/3/2019 for

12 days), and nitrofurantoin (27/3/2019 for 3 days). The addition of nitrofurantoin was guided by urine culture and sensitivity results. Of note is that there was a changeover of the multidisciplinary teams during this participant's hospital stay (the changeovers usually occur at the beginning of every month).

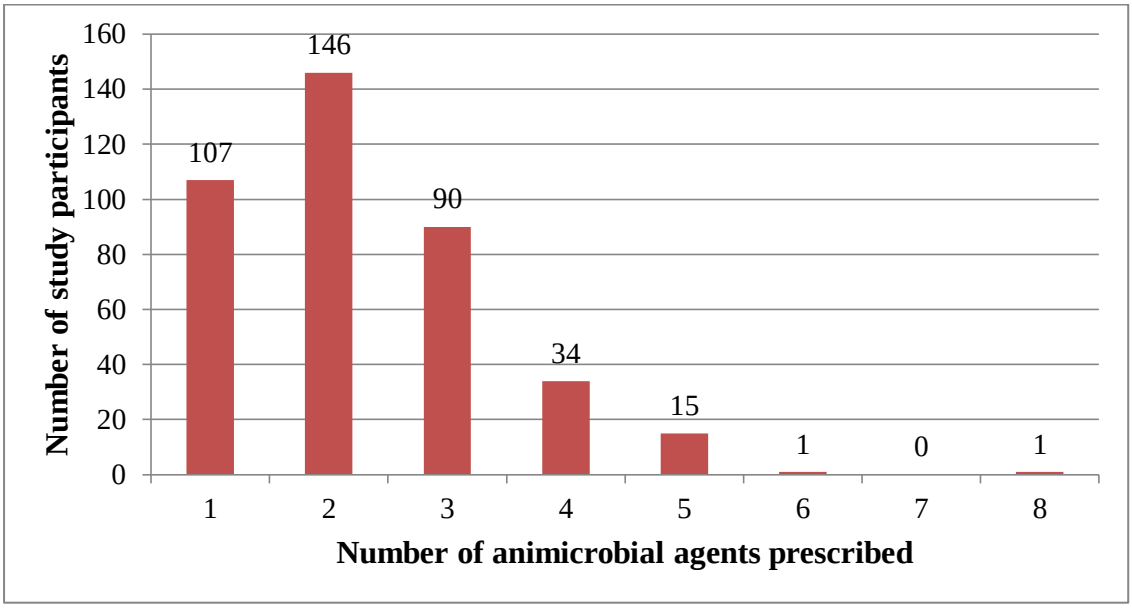

Figure 3: Number of antimicrobials prescribed per hospitalization

4.3.3 Indicator 8. Percentage of antimicrobials prescribed consistent with the formulary list

The formulary list used for deriving this indicator was the Kenya Essential Medicines List (KEML) 2016 version. Of 894 antimicrobial agents prescribed, 814 (91.1%) were present in the KEML 2016 (Table 6).

The 80 antimicrobial prescriptions that were not on the formulary list were: cefepime (35), meropenem (30), piperacillin/tazobactam (14), and itraconazole (1).

Table 6: Distribution of antimicrobials prescribed according to the national formulary list (Kenya Essential Medicines List 2016)
See Table H4 in Appendix (page 70) for a more comprehensive table of specific antimicrobials prescribed according to Kenya Essential Medicines List 2016.

No	Antimicrobial class	Number of antimicrobials	Frequency (n, %)	On KEML 2016		Specific agents not included in the KEML 2016 list
				Present (n, %)	Absent (n, %)	
1	Antibacterials	24	758 (84.8%)	679	79	Cefepime, Meropenem, Piperacillin/tazobactam
2	Antifungals	4	69 (7.7%)	68	1	Itraconazole
3	Antiparasitics	5	39 (4.4%)	39	0	-
4	Antivirals	1	28 (3.1%)	28	0	-
	TOTAL	34	894 (100%)	814 (91.1%)	80 (8.9%)	

4.3.4 Indicator 9. The average cost of antimicrobials prescribed per hospitalization in which antimicrobials were prescribed

Among the 394 study participants, the antimicrobial agents prescribed accounted for a total sum of KShs. 2,256,821.00/= (Table **7**). Therefore, the average cost of antimicrobials prescribed per hospitalization was KSh. 5,727.97/=, equivalent to USD 52.14. The dollar to Kenyan shilling conversion was done according to the prevailing foreign exchange rate of 109.83.

Table 7: Cost of antimicrobials prescribed among the 394 study participants

	Antimicrobial class	Number of antimicrobials prescribed (n, %)	Total doses of prescribed (n, %)	The total cost of prescribed treatment (KShs.)	Percentage cost
1	Antibacterials	758 (84.8%)	10,499 (81.6%)	2,099,047/=	93.0%
2	Antifungals	69 (7.7%)	794 (6.2%)	80,106/=	3.5%
3	Antiparasitics	39 (4.4%)	512 (4.0%)	21,640/=	1.0%
4	Antivirals	28 (3.1%)	1,068 (8.3%)	56,028/=	2.5%
	TOTALS	**894 (100%)**	**12,873**	**2,256,821.00**	**100.0%**

See Table H5 in Appendix (page 71) for a more comprehensive table on the cost of prescribed antimicrobials for specific antimicrobial agents.

The top five antimicrobial agents with the highest percentage costs were meropenem, ceftriaxone, piperacillin/tazobactam, vancomycin, and linezolid. The high percentage costs for meropenem, piperacillin/tazobactam, vancomycin, and linezolid were due to high unit costs, while ceftriaxone was due to a high rate of consumption (Appendix-Table H5).

4.3.5 Indicator 10. The average duration of prescribed antimicrobial treatment

The days of therapy were defined as "the number of days that a study participant received an antimicrobial agent, regardless of dose" (Ibrahim & Polk, 2014). This calculation assesses the total burden of antimicrobial use as it considers the number of agents given and the number of days of antimicrobial exposure.

The total number of days on antimicrobial agents for all the 394 study participants was 6098 days. Therefore, an average duration of prescribed antimicrobial treatment per hospitalization was 15.5 days (median=10.5). The duration of treatment per antimicrobial agent prescribed was 6.82 days (median=5 days) (derived from 6098 total days of treatment for 894 antimicrobials prescribed) (Appendix-Table H6 on page 73). This reinforces the finding of Indicator 7 that points towards the use of combination therapy (2.3 antimicrobial agents) per hospitalization.

The length of therapy, defined as "the number of days that a patient receives systemic antimicrobial agents, irrespective of the number of different drugs" (Ibrahim & Polk, 2014), was 8.2 days per hospitalization (derived from the total length of therapy for the study population of 3228 days).

4.3.6 Indicator 13. Percentage of patients with pneumonia who are prescribed antimicrobials in accordance with STGs

The study participants identified for this indicator had a written diagnosis of pneumonia in their medical records. There was a total of 101 (26%) study participants who had pneumonia. Since there were no hospital standard treatment guidelines for MTRH, the guidelines used to assess this indicator was: the Kenya clinical guidelines (MOH, 2009), the British Thoracic Society guidelines (Lim et al., 2009), Infectious

Diseases Society of America, and American Thoracic Society 2019 guidelines (Metlay et al., 2019).

Of the 101 study participants diagnosed with pneumonia in their medical records, 99 were treated according to STGs. Therefore, the percentage of patients with pneumonia who are prescribed antimicrobials in accordance with STGs was 98%. Among the 101 study participants with pneumonia, 219 antimicrobial agents (average = 2.19, median =2). Ceftriaxone was the most commonly prescribed antimicrobial agent (Figure 3), while ceftriaxone and azithromycin were the most frequently prescribed combination therapy.

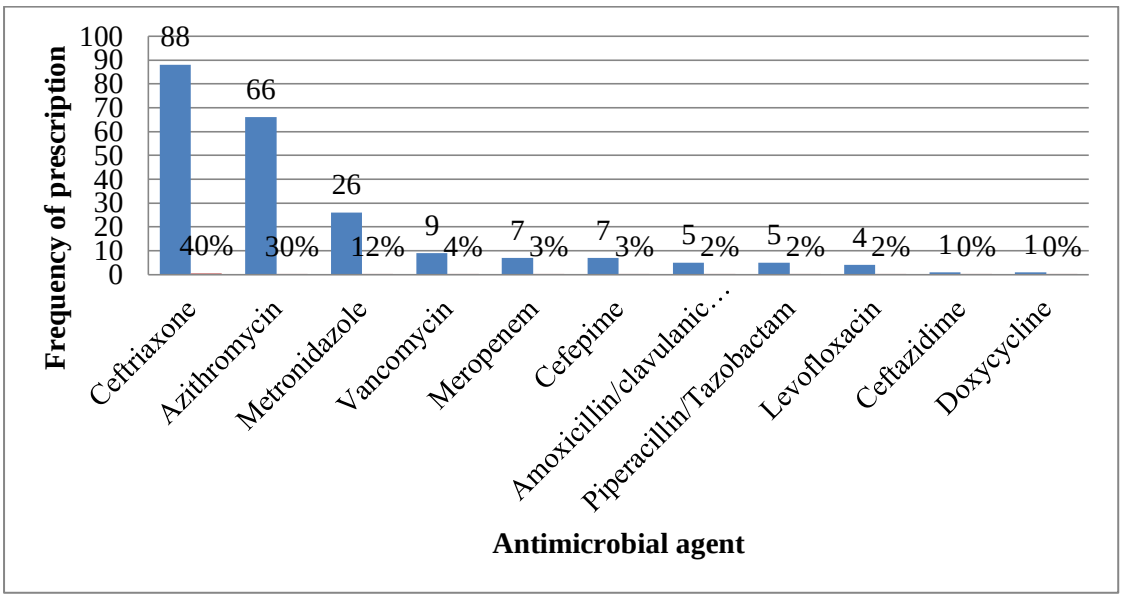

Figure 4: Antimicrobial agents used among the study participants with pneumonia

4.3.7 Indicator 14. Percentage of antimicrobials prescribed by generic name

There were 894 prescribed antimicrobial agents for the study population; generic names were used for 777 (86.9%) antimicrobial agents (Table 8). Metronidazole was the drug most frequently prescribed by brand name as Flagyl®

Table 8: Antimicrobial agents prescribed by brand name

	Antimicrobial class	Frequency of antimicrobial agents	Prescribed by generic name		Specific antimicrobials prescribed by brand name
			Yes	No	
1	Antibacterials	758	645	113	Amoxicillin/Clavulanic acid (Augmentin®) (7)
					Ceftriaxone (Rocephin®) (4)
					Cefuroxime (Zinacef®) (1)
					Clindamycin (Dalacin-C®) (1)
					Flucloxacillin (Floxapen®) (14)
					H. pylori kit (Esokit®) (2)
					Metronidazole (Flagyl®) (72)
					Cotrimoxazole (Septrin®) (12)
2	Antifungals	69	69	0	-
3	Antiparasitics	39	35	4	Paromomycin (Aminosidine, Gabbroral®) (4)
4	Antivirals	28	28	0	-
	TOTALS	894	777	117	

4.3.8 Summary of study findings of 6 prescribing indicators

Table 9: Prescribing indicators summary of findings

Indicator No.	Indicator description	Findings	WHO recommendations
7	The average number of antimicrobials prescribed per hospitalization in which antimicrobials were prescribed	2.3 antimicrobials (median=2)	-
8	Percentage of antimicrobials prescribed consistent with the hospital formulary list	91.1%	100%
9	The average cost of antimicrobials prescribed per hospitalization in which antimicrobials were prescribed	KShs. 5,727.97/= USD 52.14	-
10	The average duration of prescribed antimicrobial treatment	15.5 days (median=10.5), and *LOT of 8.2 days	7-10 days
13	Percentage of patients with pneumonia who are prescribed antimicrobials in accordance with standard treatment guidelines	98%	100%
14	Percentage of antimicrobials prescribed by generic name	86.9%	100%

*LOT- Length of therapy

4.4 Description of Patient Care Indicators

4.4.1 Indicator 15. Percentage of doses of prescribed antimicrobials actually administered

The 894 antimicrobials prescribed worked out to 12873 doses (working from the frequency per day and duration). On the treatment sheet, only 8663 doses (67.3%) were ticked as actually administered (Table 10) based on the presence of a tick and the signature of the person administering.

Table 10: Doses of antimicrobial agents prescribed actually administered

	Antimicrobial class	Number of antimicrobials	Doses prescribed	Doses administered	Percentage
1	Antibacterials	758	10,499	7,229	68.9%
2	Antifungals	69	794	602	75.8%
3	Antiparasitics	39	512	234	45.7%
4	Antivirals	28	1,068	598	56.0%
TOTALS		**894**	**12,873**	**8,663**	**67.3%**

See Table H7 in Appendix (page 75) for a more comprehensive table on the distribution of percentages for specific antimicrobial agents prescribed actually administered

4.4.2 Indicator 16. The average duration of hospital stay of patients who receive antimicrobials

The total number of hospitalization days for the 394 study participants was 4812 days, which yielded an average duration of hospital stay for the study population of 12.2 days (median= 10 days). More than half the study participants had a hospital stay up to 10 days (Table 11).

Table 11: Duration of hospital stay for the study participants

Duration of hospital stay (days)	Number of study participants (n, %)
1-10	208 (52.8%)
11-20	120 (30.4%)
>20	66 (16.8%)
Total days of hospital stay = 4812	Total study participants= 394

4.5 Description of Supplemental Indicator

4.5.1 Indicator 17. Number of antimicrobial drug sensitivity tests reported per hospital admission

The hospital laboratory routinely performed culture and sensitivity tests. Eighty-three (83) samples were taken for culture among the study participants, which yielded 17 samples with microbial growth. Out of these 17 positive cultures obtained from the study population, 13 (76.5%) sensitivity tests were reported, and sensitivity-guided changes to antimicrobial treatment were made for 7(53.8%) study participants (Table 12).

Table 12: Outcomes of culture and sensitivity tests performed for the study population

	Sample type	The outcome of the culture test			Total number of tests ordered	The outcome of positive culture test	
		Positive	Negative	No results*		Sensitivity test	Change of antimicrobial agent
1	Cerebrospinal fluid	3	43	0	46	1	0
2	Blood	4	5	7	16	3	2
3	Urine	7	2	0	9	6	3
4	Pleural fluid	0	5	0	5	0	0
5	Ascitic fluid	0	3	0	3	0	0
6	Pus	2	0	0	2	2	1
7	Sputum	1	0	1	2	1	1
TOTALS		**17**	**58**	**8**	**83**	**13**	**7**

* No results were present in the study participant's medical records as at the time of data collection

4.6 Summary of findings for patient care and supplemental indicators

Table 13: Patient care and supplemental indicators summary findings.

Indicator no.	Indicator description	Study findings	WHO recommendation
Patient care indicators			
15	Percentage of doses of prescribed antimicrobials actually administered	67.3%	100%
16	The average duration of hospital stay of patients who receive antimicrobials	12.2 days (median=10)	-
Supplemental indicators			
17	Number of antimicrobial drug sensitivity tests reported per hospital admission with antimicrobials prescribed	20.1% study participants had culture test done. Of 17 positive culture tests, 76.5% had sensitivity tests reported	-

CHAPTER FIVE: DISCUSSION

The antimicrobial use indicators were developed under the rational pharmaceutical management program to detect issues concerning antimicrobial usage in a hospital, which is an essential precursor to instituting actions towards stemming of antimicrobial resistance. These indicators allow for comparisons of antimicrobial use between hospitals or within a hospital over different periods. The results should be interpreted in the context of the hospital level and complexity since reference ranges for the indicators have not been established. Further investigations may be required to reveal the underlying causes of the problems identified (MSH, USAID, 2012).

5.1 Hospital indicators

Vigilant management of antimicrobial agents is crucial to hospitals as its use has clinical and economic implications.

Drugs and Therapeutics Committees (DTCs) provide guidance and mechanisms for selecting medicines listed in a formulary, identifying medicine use problems, reduction of medicine cost, and support for rational medicine use through the development of guidelines or policies for management of drug use (Serveur, 2004). Drug and Therapeutics Committees are also mandated to conduct regular reviews of these crucial policy documents (every 3 years for standard treatment guidelines and every 2 years for formulary lists) (MSH, USAID, 2012). Drug and Therapeutics Committees (DTCs) have existed in resource-rich countries such as the United States since the 1930s and were introduced in developing countries in 1975 to improve the rational use of medicines (Weltgesundheit, 1978). A review of the existence and interventions of DTCs in 5 African countries was conducted by Management Sciences for Health (MSH). There were 496 DTCs in total. Some of the published interventions by the DTCs were drug utilization studies conducted in Gauteng Province in South

Africa, quality improvement programs on antimicrobial use in Swaziland, ceftriaxone use policies, and sensitization of health workers on malaria management guidelines in Ethiopia. In Kenya, though many hospitals have DTCs, published work is available for hospitals in Migori county for quality improvement interventions on malaria case management, Kakamega county on the implementation of prescription errors recording book, and Nyeri county on sensitization of healthcare providers and staff on rational use of antibiotics, implementation of ceftriaxone restriction policy, and regular antibiotic audits (Getahun et al., 2015). Drug and Therapeutics Committees in Kenyatta National Hospital (KNH) launched their hospital formulary lists in September 2013 (Omonge, 2013), and Kenyatta University Teaching, Referral, and Research Hospital (KUTRRH) in August 2022 (Dagane, 2022). Though a DTC exists at Moi Teaching and Referral Hospital (MTRH), it was not as active as recommended by World Health Organization (WHO). The WHO suggests that DTC meetings occur monthly or quarterly. There were also no standard treatment guidelines (STGs) for infectious diseases and no hospital formulary list (FL) (the hospital FL was last updated in 2010). These findings are similar to those reported in an Ethiopian study. The study site was a tertiary and teaching hospital with physicians who manage patients based on expertise. Therefore, the antibiotic options may not be limited to those in STGs (Demoz et al., 2020).

In contrast, a study in India done in a tertiary care hospital (56 physicians) had no mention of a DTC. Still, it had annually revised STGs (50 infectious diseases listed) and an up-to-date hospital-specific formulary list (Nia et al., 2018). A study in South Africa found some challenges with the running of DTC activities to be staff shortage (35%), poor meeting attendance (30%), poor communication of decisions (20%), and lack of time allocated for meetings (20%) (Matlala et al., 2017). A qualitative study

carried out in 3 countries (MTRH was one of the study sites for Kenya) revealed that physicians highly recommended formulating hospital-specific guidelines by a multidisciplinary team. The physicians recommended periodic guideline reviews at 3, 6, and 12 months to improve antimicrobial prescription patterns (Rolfe et al., 2021). Maina et al. (2020) demonstrated disease conditions of interest when developing STGs in a study that included 14 hospitals in Kenya. These were pneumonia, Human Immunodeficiency Virus (HIV) infection, pulmonary tuberculosis, central nervous system infections, and malaria (specific to the adult medical wards) (Maina et al., 2020).

Rational prescribing is dependent on the availability of required antimicrobials. The clinical impact of lack of antimicrobial agents is the risk of increased morbidity and mortality. Quantifying the days out of stock for antimicrobials measures the probability that an antimicrobial agent was out of stock over the study period. This indicator, therefore, assesses the hospital's ability to maintain a constant supply of antimicrobials.

The World Health Organization (WHO) recommends that medicines in an essential medicines list are available and there be no stock-outs. In this study, the availability of antimicrobial agents was low (62.6%), with frequent days out of stock (8.68 days per month on average). A study in Ethiopia (Demoz et al., 2020) had similar findings of low availability of antimicrobial agents (65.2%) but fewer days out of stock (3.8 days per month). In both MTRH and the Ethiopian study, there were no formulary lists. The hospital in the Ethiopian study procured all its medicines from the government supplier hence a more reliable supply of medicines and fewer stock-outs. In the national referral hospitals in Kenya such as MTRH, procurement of medicines id done through private tenders and financed through grant, compared with county hospitals

that rely on the government supplier (Toroitich et al., 2022). For prescribers, the implication of lack of key antimicrobials is the selection of less suitable antimicrobial agents that may have higher costs and less favorable side effect profiles (Amaha et al., 2018). Some of the postulated barriers to access anti-infective agents in low and middle-income countries include inadequate supply chain systems, poor health financing, regulatory barriers that hinder market entry (Center for Disease Dynamics, Economics & Policy, 2019). Another barrier to access to preferred antimicrobial agents is the lack of antimicrobials recommended on culture and sensitivity reports, leading to the selection of less suitable antimicrobial agents for managing infections (Rolfe et al., 2021).

In contrast, a study in Pakistan (Atif et al., 2017) had high availability of antimicrobial agents (93.8%), a few days out of stock (3.3 days per month), and a low expenditure of antimicrobial agents (12.2%). This hospital in Pakistan had an annually updated formulary list that facilitated better availability of antimicrobials. The supply of drugs was fully government-funded, leading to fewer days out of stock. However, the expenditure was likely underestimated since only one-time annual bulk purchase data were available (data from multiple and local purchase orders were not readily accessible for use in the study). Pakistan has a robust pharmaceutical sector with 759 manufacturing units and meets 70% of the country's pharmaceutical drug needs. Therefore, the country can maintain reliable stock levels and keep drug costs relatively low (PPMA, 2016), while Kenya largely relies on imports, which present supply chain challenges in price and accessibility (Toroitich et al., 2022).

5.2 Prescribing Indicators

The prescribing indicators measure the performance of prescribers in areas of the appropriate use of medicines. The average number of antimicrobials prescribed per

hospitalization measures the degree of antimicrobial use. The national antimicrobial stewardship guidelines for healthcare settings in Kenya (MOH, 2020b) recommend that the initial management of infections require antimicrobial agents with a broad spectrum of activity. It is prudent to deescalate (switch from combination therapy to monotherapy). Continuing with a broad spectrum regimen does not necessarily ensure better outcomes and enhances antimicrobial resistance (MOH, 2020b). The findings of this study (2-3 antimicrobials prescribed per hospitalization) was similar to a study in India (Nia et al., 2018) and higher than the study in Pakistan (1-2 antimicrobials prescribed per hospitalization) (Atif et al., 2017). Since there are no WHO-recommended parameters for this indicator, studies done over time may assist the hospital in identifying an acceptable range.

Compliance with policies and guidelines to guide the treatment of patients cannot be overemphasized. The WHO recommends that hospitals have full (100%) compliance with the formulary list. In this study, compliance with Kenya Essential Medicines List version 2016 was not ideal (91.1%). The KEML 2016 version was under review at the time of data collection, and a newer version was published in 2019 after data collection was complete. More and newer antimicrobials were included in the 2019 version compared to the 2016 version. This means the hospital may have been ahead of the Ministry in reviewing its formulary list especially because it is a major referral hospital. The findings contrast with two studies done in Eritrea (Amaha et al., 2018) and Ethiopia (Demoz et al., 2020), which had 100% compliance with their national essential medicines list. All medicines were purchased from one supplier who only used the national essential medicines list to procure medicines in both these studies. In previously cited studies in India (Nia et al., 2018) and Pakistan (Atif et al., 2017),

both hospitals had formulary lists that were updated annually, and the compliance with the hospital formulary was high (100% in India and 99.45% in Pakistan).

Various prescribing practices (such as the number of antimicrobials, dosage, duration of antimicrobial therapy) influence the average cost of antimicrobials per hospitalization. Since the Kenya National Hospital Insurance Fund (NHIF) population coverage is still low at 14% (Barasa et al., 2018), healthcare costs are often paid from patients' pockets. The subsistence or poverty level (income that only caters to an individual's basic needs)

in Kenya is between Kenya shillings (Kshs) 3,252 (rural) and 5,995 (urban) per month per person (World Bank, 2020). Half (50%) of Kenyan households earn less than KShs. 10,000/- per month, and 2% have no income (Mbogo, 2018). Therefore, the cost of antimicrobial treatment derived from this study (KSh. 5,727.97/=) is high. The impact of these healthcare costs and may be financially debilitating for families. The study in India had a higher cost of antimicrobials (USD 140) per hospitalization (Nia et al., 2018). The hospital's formulary list had a wide selection of antimicrobials (98) listed as brand and generic names. This allowed prescribers to select more expensive brand antimicrobial agents. In MTRH, the KEML in use has listed all medicines by generic names only, allowing for procurement of cheaper generic drugs hence containing the cost of antimicrobial agents. The MTRH study findings can also be contrasted with a previously cited study in Pakistan with a lower cost of antimicrobials (USD 6.25). The Pakistan study's significantly lower cost of antimicrobials can be attributed to the vibrant pharmaceutical manufacturing industry (Atif et al., 2017).

The average duration of prescribed antimicrobial treatment measures the intensity of antimicrobial exposure during hospitalization (MSH, USAID, 2012). In this study, the

average antimicrobial exposure was 8.2 days. These findings contrast with a study done in India that per hospitalization had a shorter treatment duration (5.65 days) (Nia et al., 2018). Prescribing at the Indian hospital was guided by hospital standard treatment guidelines (STGs) that standardize infectious diseases' management. At MTRH, there were no STGs for infectious diseases, and treatment decisions were based on the clinician's discretion. A survey conducted in 3 sites in the southeastern United States of America (USA) had duration of inpatient antimicrobial use of 3 days (median) which is a third of the findings of this study. The study sites in the USA had robust antimicrobial stewardship programs in place and extensive electronic health records (Dyer et al., 2019).

Quality of patient care can be measured by assessing whether a common infectious disease (pneumonia) management is in line with standard treatment guidelines (STGs). In this study, 98% of study participants were treated in accordance with Kenya National and selected international STGs. This finding contrasts with two studies carried out in India (Nia et al., 2018) and Pakistan (Atif et al., 2017) that had much lower levels of compliance of 19.23% (26 patients with pneumonia), and noncompliance (0%) for Pakistan (7% of patients with pneumonia). For the India study, compliance was measured against its own hospital standard treatment guidelines, whereas for the MTRH and Pakistan studies, since STGs were not available, compliance was measured against international guidelines. However, the Pakistan study only used guidelines for community-acquired pneumonia (Mandell et al., 2007) which may have led to the low adherence to guidelines seen, while in this study, several guidelines (both national and international) were used that had treatments for the various types of pneumonia hence showed high adherence. A limitation with this WHO indicator (percentage of patients with pneumonia who are

prescribed antimicrobials in accordance with STGs) is that it does not specify which type of pneumonia would be assessed therefore causing the differences in results across different study settings.

Prescribing by generic name simplifies dispensing since it allows generic substitution and improves hospital efficiency (procurement). The WHO recommends 100% prescribing by generic name (MSH, USAID, 2012). This was not achieved in this study (86.9%). The adherence to prescribing by generic name was low in two studies: 13.18% in India (Nia et al., 2018) and 19.5% in Pakistan (Atif et al., 2017). The reason behind this low prescribing by generic name in Pakistan was not apparent since the formulary list contained 25 antimicrobial agents, all listed by generic name. In India, the low level of prescribing by generic name may have been encouraged by the formulary list that had 98 antimicrobials listed by both brand and generic name).

A systematic review detailing the impact of physician-pharmaceutical sales representative interactions showed that offering incentives (free drug samples, continuous medical education sponsorship) led to increased prescribing by brand name rather than a generic name (Fickweiler et al., 2017).

5.3 Patient Care Indicators

To effectively manage infectious diseases, all doses of antimicrobial agents prescribed must be administered, which affects the rate of recovery from the infection and may influence the duration of hospital stay. One of the patient care indicators measures the extent to which the antimicrobials actually reach the patient and is calculated assuming that administered medicines are recorded on the patient's treatment record. In this study, there was a low percentage of prescribed antimicrobial doses administered (67.3%). The percentage of missed doses (32.7%) in this study is similar to that of the Ethiopian study, with 30% of missed doses largely attributed to stock-

outs (Fenta et al., 2020). Other possible reasons for the low percentage of prescribed doses administered may be a human error (dispensing or nursing) and lack of qualified staff (MSH, USAID, 2012). Physicians interviewed from low and middle-income countries (including MTRH), under the theme of discrepancies between desired and actual antimicrobial treatment, opined that nursing staff was crucial in delivering antimicrobials (Rolfe et al., 2021).

Duration of hospital stay is an important indicator that assesses the efficiency of hospital management and quality of patient care. A short duration of hospital stay has been linked to decreased adverse effects of medications, fewer opportunistic infections, and improved outcomes (Baek et al., 2018). The duration of hospital stay in this study(12.2 days: median=10 days) was longer compared to two similar studies: 6.98 days in India (Nia et al., 2018) and 5.9 days in Pakistan (Atif et al., 2017).

In this study, antibacterial agents 758 (84.8%) accounted for the largest class of antimicrobials prescribed. Antimicrobial agents most frequently prescribed were ceftriaxone (33.5%), azithromycin (11.4%), and metronidazole (9.8%). In a global point prevalence study done in a regional hospital in Kenya, the most frequently prescribed antimicrobials were ceftriaxone (39.7%), benzylpenicillin (29.0%), and metronidazole (25.1%) (Momanyi et al., 2019). These findings differ from those in other countries, such as in Eritrea, where ampicillin 42.1%, benzylpenicillin 13.7%, gentamycin 9.8% were the most commonly prescribed antibiotics (Amaha et al., 2018). In the Democratic Republic of Congo, ampicillin was the most prescribed antimicrobial agent, while amoxicillin was the most prescribed in Zambia (Amaha et al., 2018). This inconsistency may be because this study was carried out in a national referral hospital that serves patients likely to be referred from other health care facilities. Therefore, the prescribers may utilize antimicrobial agents with lower rates

of antimicrobial resistance to manage complex medical conditions, as seen in the Eritrean study (Amaha et al., 2018). A qualitative study done in MTRH and other hospitals in low and middle income countries elucidated that the physician's choice of antimicrobial therapy was influenced by existing practices of unrestricted access to antimicrobials in the community (over-the-counter access to antimicrobials) and in private facilities which hinders rational antimicrobial prescribing (Rolfe et al., 2021).

5.4 Supplemental Indicator

Sensitivity data of microorganisms that cause infections are crucial for selecting effective therapy with antimicrobial agents (MSH, USAID, 2012). In this study, 20.1% of the study participants had culture tests reported. The number of antimicrobial drug sensitivity tests reported out of the positive cultures (17) was 13 (76.5%). This finding is higher than a Pakistan study with 2 (0.24%) sensitivity tests reported, signifying largely empiric prescribing (Atif et al., 2017). The previously cited Ethiopian study done in a tertiary hospital indicated that the hospital did not carry out culture and sensitivity tests; hence antimicrobial prescriptions were fully empiric, and mainly broad-spectrum antibiotics were used (Demoz et al., 2020). Some of the barriers to uptake of antimicrobial sensitivity tests, also noted in MTRH, include long turnaround time for results, staffing shortages, lack of confidence in laboratory services, lack of communication between clinicians and laboratory personnel, inadequate sharing of antimicrobial resistance data (MOH, 2020b) (Rolfe et al., 2021).

5.5 Study Limitations

There is a lack of WHO recommendations or reference values for many of the specific indicators for hospitalized patients, hence difficulty assessing whether antimicrobial use was optimal. However, this study forms a good baseline study for comparison of future trends.

The WHO indicator for management of pneumonia patients according to standard treatment guidelines did not specify the type of pneumonia to be investigated. This presented challenges when compared with other studies that only assessed for one type of pneumonia.

The antimicrobials use indicators were not all-inclusive. Therefore, other aspects of antimicrobial consumption in hospitals were not measured.

CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

1. There were no hospital-specific standard treatment guidelines for infectious diseases, no up-to-date formulary list, low availability of antimicrobials on the selected day of study (62.6%), and frequent stock-outs of antimicrobial agents (8.68 days/month).
2. Between 2-3 antimicrobial agents were used per patient per hospitalization, high treatment costs (USD 52.14), and low prescribing by generic name 86.9%.
3. The administration of antimicrobial doses prescribed was low (67.3%).
4. Prescribing of antimicrobials was largely empiric, with few culture tests done per hospitalization.

6.2 Recommendations

6.2.1 Recommendations for policy and practice

There is a need to optimize antimicrobial use at Moi Teaching and Referral Hospital (MTRH). Some of the strategies that may be employed include:

1. Update the hospital formulary, draft and promote the use of STGs and fully implement generic name prescribing.
2. Increase availability of antimicrobials and reduce stock-outs
3. Ensure 100% of the prescribed drugs are administered to patients and promote prescribing based on culture and sensitivity tests

6.2.1 Recommendations for future research

A root cause analysis and possible solutions to the gaps identified

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APPENDICES

Appendix A: Instrument 1 (Basic information)

This instrument collects information for Indicators 1 and 2

Name of unit:_____Data collector:_____Date: _____

1. Does the hospital have a Drug and Therapeutics Committee? ☐ Yes ☐ No

2. If affirmative, when was the last meeting?_____

3. Does the hospital have a formulary list or EML authorized for the acquisition of medicines by the hospital? ☐ Yes ☐ No

4. Date of last revision of the formulary list or EML? _____

5. If yes, how many antimicrobials are on the formulary list or EML? _____[Request a copy of the list.]

6. Are all of the medicines on the formulary list identified by generic name (INN)? ☐ Yes ☐ No

7. Are the formulary or EML medicines based on those recommended in the STG? ☐ Yes ☐ No

8. Does the hospital have standard treatment guidelines (STGs) for infectious diseases for the most prevalent conditions? ☐ Yes ☐ No For pneumonia? ☐ Yes ☐ No [Request a copy.]

9. Date of last revision of the STGs for infectious diseases? _____

10. How many infectious disease treatments are listed in the STGs? _____

11. Does the hospital laboratory routinely perform antimicrobial drug sensitivity tests (antibiograms, cultures)? ☐ Yes ☐ No

12. How much did the hospital spend on medicines last year? _____

13. How much was budgeted or allotted for medicines by the hospital or Ministry of Health last year?

Appendix B: Instrument 2 (Availability of a set key of antimicrobials and time out of stock)

This instrument collects information for Indicator 3 and 4

1	2	3	4	5	6
		Days Out Of Stock			
Product (Generic Name, Form, and Strength)	Current Stock	Month 1	Month 2	Month 3	Total Days Out of Stock
					Total:

Appendix C: Instrument 3 (Cumulative purchase of antimicrobials)
This instrument collects information for Indicator 5

Name of unit:_____Data collector:_____Date:_____

1	2	3	4
Generic Name of Antimicrobial	Total Cost of Antimicrobial	Percentage of Total	Cumulative Percentage
	Total:		

Appendix D: Instrument 4 (Antimicrobials purchased)
This instrument collects information for Instruments 3 and 5 and Indicator 9

Name of unit:_____Data collector:_____Date:_____

Generic name of the antimicrobial: _____

1	2	3	4	5	6
Generic or Brand Name	Dosage Form and Strength	Dispensing Unit	Unit Cost	Quantity	Total Cost
				Total Cost of Antimicrobials:	

Generic name of the antimicrobial: _____

1	2	3	4	5	6
Generic or Brand Name	Dosage Form and Strength	Dispensing Unit	Unit Cost	Quantity	Total Cost
				Total Cost of Antimicrobials:	

Appendix E: Instrument 5 (Form to record antimicrobial treatments)

Patient Information			Antimicrobial Information												
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Clinical Study No.	Pneumonia Case? (*Y*/N)	No. of Days in Hospital	Was Sensitivity Test Done? (*Y*/N)	Name(s) of Antimicrobial(s) Prescribed	INN Used? (*Y*/N)	Antimicrobial on FL? (*Y*/N)	Dosage Form and Strength	Total of Days of Treatment	No. Antimicrobials of Same Generic Type Prescribed	Dosage Frequency per Day	Doses Prescribed	Doses Administered	Unit Cost of Dose	Cost of Prescribed Treatment	Cost of Administered Treatment
Total Cases	Total *Ys*	Total Days	Total *Ys*	Total	Total *Ys*	Total *Ys*		Total Days	Total Generics		Total Doses	Total Doses		Total Cost	Total Cost

This instrument collects information for Indicators 7, 8, 9, 10, 13, 14, 15, 16 and 17

Name of unit:_____Data collector:_____Date: _____

Notes:

No. = number, Y = Yes, N = No, INN = international nonproprietary name, FL = formulary list, * = TB treatment provided by national Ministry of Health program funded by PEPFAR **=HIV treatment provided by national Ministry of Health Program funded by PEPFAR

Appendix F: Informed consent form

MOI UNIVERSITY COLLEGE OF HEALTH SCIENCES / MOI TEACHING AND REFERRAL HOSPITAL

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC) INFORMED CONSENT FORM (ICF)

Study Title: PATTERN OF USE OF ANTIMICROBIAL AGENTS IN THE ADULT MEDICAL WARDS, MOI TEACHING AND REFERRAL HOSPITAL

Name of Principal Investigator(s): Roselyne K. Moin

Name of Organization: Moi University, P.O Box 3900-30100 Eldoret, Uasin Gishu County, Kenya. Hotline: +254 790940508

Informed Consent Form for Adult patients undergoing treatment with antimicrobial agents in the adult medical wards

This Informed Consent Form has two parts:

• Information Sheet (to share information about the study with you)

• Certificate of Consent (for signatures if you choose to participate)

You will be given a copy of the signed Informed Consent Form

Part I: Information Sheet

Introduction:

You are being asked to take part in a research study. This information is provided to tell you about the study. Please read this form carefully. You will be given a chance to ask questions. If you decide to be in the study, you will be given a copy of this consent form for your records.

Taking part in this research study is voluntary. You may choose not to take part in the study. You could still receive other treatments. Saying no will not affect your rights to health care or services. You are also free to withdraw from this study at any time. If you choose to quit after data collection, you can request that the information provided by you be destroyed under supervision- and thus not used in the research study. You will be notified if new information becomes available about the risks or benefits of this research. Then you can decide if you want to stay in the study

Purpose of the study:

The study aims to determine how antimicrobial agents are used among hospitalized patients in MTRH using four main indicators. The first is the hospital indicator that looks at the availability of standard treatment guidelines and funding of antimicrobial agents. The second indicator is the prescribing indicator, which addresses different aspects of prescribing such as drug selected, duration of use, route of administration, as well as cost. The third indicator is the patient care indicator which assesses the length of hospital stay. The last indicator, the supplemental indicator, checks whether drug sensitivity tests are done.

Type of Research Project/Intervention:

This research will be an observational type of study which means that there will be no interventions to your medical care

Why have I been identified to Participate in this study?

You were selected through the use of the ward's admission book. The book contains a list of all the admissions.

How long will the study last?

You will be in this study up to the date you are discharged as long as you are in the hospital for less than a month. You will exit the study on the 31st day if you stay in the hospital exceeds a month.

What will happen to me during the study?

We are asking you to help us learn more about how antimicrobial agents are used in adult medical wards. If you accept, you will be asked to allow us to record various aspects of your care concerning antimicrobial agents used from the time of your admission to the time of discharge.

Are there benefits to taking part in the study?

The possible benefits to society may include helping to implement policies for the appropriate use of antimicrobial agents. There are no direct benefits to the participant.

Who do I call if I have questions about the study?

Questions about the study: Roselyne Moin at roselynemoin@gmail.com

Questions about your rights as a research subject: You may contact Institutional Review Ethics Committee (IREC) 053 33471 Ext.3008. IREC is a group of people that reviews studies for safety and to protect the rights of study subjects.

Will the information I provide be kept private?

All reasonable efforts will be made to keep your protected information (private and confidential. Protected Information is information that is, or has been, collected or maintained and can be linked back to you. Using or sharing ("disclosure") of such information must follow National privacy guidelines. By signing the consent document for this study, you are giving permission ("authorization") for the uses and disclosures of your personal information. A decision to take part in this research means that you agree to let the research team use and share your Protected Information as described below.

As part of the study, Roselyne Moin and her study team may share portions of your medical record with the groups named below:

- The Institutional Review and Ethics Committee
- Hospital administration

National privacy regulations may not apply to these groups; however, they have their policies and guidelines to assure that all reasonable efforts will be made to keep your personal information private and confidential.

The study results will be retained in your research record for at least six years after the study is completed. At that time, the research information not already in your medical record will be destroyed. Any research information entered into your medical record will be kept indefinitely

Unless otherwise indicated, this permission to use or share your Personal Information does not have an expiration date. If you decide to withdraw your permission, we ask that you contact Roselyne Moin in writing and let her know that you are withdrawing your permission. The mailing address is roselynemoin@gmail.com. At that time, we will stop further collection of any information about you. However, the health information collected before this withdrawal may continue to be used for reporting and research quality.

Your treatment, payment, or enrollment in any health plans or eligibility for benefits will not be affected if you decide not to take part. You will receive a copy of this form after it is signed.

Part II: Consent of Subject:

I have read or have had read to me the description of the research study. The investigator or his/her representative has explained the study to me and has answered all of the questions I have at this time. I have been told of the potential risks, discomforts, and side effects as well as the possible benefits (if any) of the study. I freely volunteer to take part in this study.

_____ _____ _____

Name of Participant Signature of subject/thumbprint Date & Time

(Witness to print if the subject is unable to write)

_____ _____ _____

Name of Representative/Witness Relationship to Subject Date

_____ _____ _____

Name of person Obtaining Consent Signature of person Date of Obtaining Consent

_____ _____ _____

The printed name of Investigator Signature of Investigator Date

Appendix G: Data collection methods for hospital, prescribing, patient care, and supplemental indicators
Section A: Hospital indicators

Table G1: Data collection procedure for hospital indicators

	Indicator description	Location of /person with information	Data sources and point in time of data collection	Data collection tool used and question answered
1	Existence of standard treatment guidelines (STGs) for infectious diseases	Drug and Therapeutics Committee chair (office of the director of clinical services)	Information on STG Time: Day 1 of study	Appendix 1: Instrument 1 (Basic information), questions 8, 9 and 10
2	Existence of an approved hospital formulary list or essential medicines list (EML)	Chief pharmacist	Information and copy of the formulary list and essential medicines list Time: Day 1 of study	Appendix 1: Instrument 1 (Basic information), questions 3,4,5,6, and 7
3	Availability of a set of key antimicrobials in the hospital stores on the day of the study	Chief pharmacist and hospital stores manager	The availability list of drugs in the hospital stores. The researcher used this list to obtain the current stock from the inventory management software in the hospital stores. Time: Day 1 of study	Appendix 2: Instrument 2 (Availability of a set of key antimicrobials and time out of stock). Column 1 (product-generic name, form, and strength) and column 2 (current stock) were filled.
4	The average number of days that a set of key antimicrobials is out of stock	Hospital store manager	The EML was used to retrieve stock control cards for each antimicrobial agent, and the stock status was evaluated over the study period to calculate the total days out of stock for each product	Appendix 2: Instrument 2 (Availability of a set of key antimicrobials and time out of stock). Columns 3, 4, and 5 were filled at the end of each month for the study period. Column 6 was computed at the end of the

			Time: end of each month for the study period	study
5	Expenditure on antimicrobials as a percentage of total hospital medicine costs	Hospital store manager	A purchase data electronic form with all invoices quoted for the study period was available on the inventory management software Time: Appendix 4 was filled at the end of each month for the study period. Appendix 3 was filled on the last day of the study	Appendix 4: Instrument 4 (Antimicrobials purchased) was filled for each active antimicrobial ingredient by generic name for the study period. The total for each was computed into Appendix 3: Instrument 3 (Cumulative purchase of antimicrobials). Column 1 (generic name) and column 2 (total costs in descending order of value) were filled from Appendix 4 data. While columns 3 and 4 were calculated after that. *Additional information:* Appendix 1, questions 11 and 12

Section B: Prescribing, patient care, and supplemental indicators

Table G2: Data collection procedures for prescribing, patient care, and supplemental indicators

	Indicator description	Data source	Data collected on Appendix 5: Instrument 5 (Form to record antimicrobial treatments)
Prescribing indicators			
7	The average number of antimicrobials prescribed per hospitalization in which antimicrobials were prescribed	Patient medical records- treatment sheet	Column 10 (number of antimicrobials of the same generic type prescribed)
8	Percentage of antimicrobials prescribed consistent with the hospital formulary list	Patient medical records (treatment sheet) and EML	Column 5 (name(s) of antimicrobial(s) prescribed) and column 7 (antimicrobial on FL/EML)
9	The average cost of antimicrobials prescribed per hospitalization in which antimicrobials were prescribed	Patient medical records and electronic stock control cards for each agent (for unit price)	Column 14 (unit cost of dose) and column 15 (cost of prescribed treatment)
10	The average duration of prescribed antimicrobial treatment	Patient medical records- treatment sheet	Column 9 (total days of treatment) was filled for each antimicrobial
13	Percentage of patients with pneumonia who are prescribed antimicrobials in accordance with standard treatment guidelines	Patient medical records- doctor's notes (for pneumonia diagnosis), treatment sheet, and STGs	Column 2 (pneumonia case? Y/N). The treatment sheet and STGs were later applied during the analysis
14	Percentage of antimicrobials prescribed by generic name	Patient medical records- treatment sheet and EML	Column 6 (INN used? Y/N)
Patient care indicators			
15	Percentage of doses of prescribed antimicrobials actually administered	Patient medical records- treatment sheet	Column 12 (doses prescribed) and column 13 (doses administered)
16	The average duration of hospital stay of patients who receive antimicrobials	Patient medical records- doctors notes (admission and discharge notes- dates noted and days tallied	Column 3 (number of days in hospital)
Supplemental indicators			
17	Number of antimicrobial drug sensitivity tests reported per hospital admission	Patient medical records- doctors notes, laboratory documents (sensitivity results)	Column 4 (was sensitivity test done? Y/N) *Additional information :* Appendix 1, question 17

Appendix H: Supplemental materials for results

Table H1: Availability of a set of key antimicrobials in the hospital stores on the day of the study

No.*	Antimicrobial name	Dosage form	Strength	Total days o/s over 3 months	Average days o/s per month
Antibacterial agents					
1	Amikacin	Injection	125mg	61	20.33
2	Amikacin	Injection	500mg	61	20.33
3	Aminosidine	Tablets	250mg	11	3.67
4	Amoxicillin/Flucloxacillin	Injection	1g	24	8
5	Cefazolin	Injection	1g	42	14
6	Cefepime	Injection	2g	34	11.33
7	Cefuroxime	Injection	750mg	49	16.33
8	Clarithromycin	Tablets	500mg	65	21.67
9	Clindamycin	Capsules	150mg	37	12.33
10	Clindamycin	Injection	300mg	35	11.67
11	Colistin	Injection	1,000,000 i.u	24	8.00
12	Dapsone	Tablets	100mg	8	2.67
13	Esclam kit	Tablets	20mg/500 mg/1g	48	16.00
14	Flucloxacillin	Injection	250mg	89	29.67
15	Flucloxacillin	Capsules	500mg	44	14.67
16	Flucloxacillin	Injection	500mg	89	29.67
17	Gentamicin	Injection	80mg	89	29.67
18	Imipenem/Cilastatin	Injection	1g	51	17.00
19	Levofloxacin	Tablets	500mg	30	10.00
20	Meropenem	Injection	1g	11	3.67
21	Metronidazole	Injection	500mg	21	7.00
22	Nitrofurantoin	Tablets	100mg	65	21.67
23	Norfloxacin	Tablets	400mg	44	14.67
24	Ofloxacin/Ornidazole	Tablets	200mg/500 mg	89	29.67
25	Phenoxymethylpenicillin	Tablets	250mg	8	2.67
26	Piperacillin/ Tazobactam	Injection	4.5g	55	18.33
27	Polymixin	Injection	5,000 i.u	49	16.33
28	Vancomycin	Injection	500mg	61	20.33
	Others (18)	-	-	0	0

	Total for antibacterials			**1294**	**9.38**
Antiparasitic agents					
29	Secnidazole	Tablets	1g	56	18.67
	Others (7)	-	-	0	0
	Totals for antiparasitics			**56**	**2.33**
Antifungal agents					
30	Amphotericin B	Injection	50mg	82	27.33
31	Fluconazole	Tablets	200mg	31	10.33
32	Itraconazole	Tablets	100mg	31	10.33
	Others (6)	-	-	0	0
	Totals for antifungals			**144**	**5.33**
Antiviral agents					
33	Acyclovir	Tablets	200mg	54	18.00
34	Acyclovir	Injection	250mg	58	19.33
35	Acyclovir	Tablets	400mg	50	16.67
36	Ganciclovir	Tablets	450mg	89	29.67
	Totals for Antivirals			**251**	**20.92**
	TOTAL FOR ALL ANTIMICROBIALS			***1745***	***8.68***

Table H2: Days out of stock for antimicrobial agents at the hospital stores over 3-month study period (Indicator 4)

No.	Antimicrobial name	Dosage form	Strength	
	Antibacterial agents			
1	Amikacin	Injection	125mg	
2	Amikacin	Injection	500mg	
3	Amoxicillin+clavulanic acid	Tablet	1g	
4	Azithromycin	Tablet	500mg	
5	Benzathine penicillin	Injection	2.4 MU	
6	Cefazolin	Injection	1g	
7	Cefepime	Injection	1g	
8	Cefixime	Tablet	400mg	
9	Ceftriaxone	Injection	1g	
10	Ceftriaxone+sulbactam	Injection	1.5g	
11	Ciprofloxacin	Injection	200mg	
12	Ciprofloxacin	Tablet	500mg	
13	Clindamycin	Capsule	150mg	
14	Colistin	Injection	1,000,000 IU	
15	Dapsone	Tablet	100mg	
16	Erythromycin	Tablet	500mg	
17	Flucloxacillin	Injection	250mg	
18	Flucloxacillin	Injection	500mg	
19	Flucloxacillin	Injection	1g	
20	Levofloxacin	Injection	500mg	
21	Meropenem	Injection	1g	
22	Metronidazole	Injection	500mg	
23	Metronidazole	Tablet	400mg	
24	Moxifloxacin	Tablet	400mg	
25	Nitrofurantoin	Tablet	100mg	
26	Ofloxacin+ornidazole	Tablet	200mg/500mg	
27	Phenoxymethylpenicillin	Injection	250mg	
28	Rifampicin	Injection	250mg	
29	Sulphamethoxazole+Trimethoprim	Tablet	480mg	
30	Vancomycin	Injection	500mg	
	Antiparasitic agents			
31	Artemether+lumefantrine	Tablet	20/120mg	
32	Artesunate	Injection	60mg	
33	Proguanil	Tablet	100mg	
34	Quinine	Injection	600mg	
35	Secnidazole	Tablet	1g	
	Antifungal agents			
36	Amphotericin B	Injection	50mg	
37	Fluconazole	Injection	200mg	
38	Fluconazole	Tablet	200mg	
39	Griseofulvin	Tablet	125mg	
40	Ketoconazole	Tablet	200mg	
	Antiviral agents			
41	Acyclovir	Tablet	400mg	
42	Ganciclovir	Tablet	400mg	

o/s-out of stock, *36 antimicrobials listed on the table have ≥1 day out of stock, while 31 antimicrobials with no days out of stock are listed as others in parenthesis

Table H3: Purchase data for antimicrobial agents at the hospital stores for the study period (Indicator 5)

	Generic name of antimicrobial	Total quantity	The total cost of antimicrobials purchased (KSh.)	Percentage cost of total
Antibacterial agents				
1	Meropenem	8,570	7,841,550.00	20.89%
2	Cefazolin	13,000	3,915,600.00	10.43%
3	Ceftriaxone	22,020	3,801,250.00	10.13%
4	Amoxicillin/clavulanic acid	128,400	3,221,261.00	8.58%
5	Cefuroxime	27,858	2,707,255.00	7.21%
6	Clindamycin	47,520	1,628,460.00	4.34%
7	Vancomycin	2,000	1,405,742.00	3.74%
8	Esclam kit	800	1,380,000.00	3.68%
9	Amikacin	3,050	1,355,350.00	3.61%
10	Ceftriaxone/sulbactam	900	1,345,500.00	3.58%
11	Piperacillin/tazobactam	1,550	1,240,000.00	3.30%
12	Linezolid	1,010	1,113,020.00	2.96%
13	Moxifloxacin	3,000	907,800.00	2.42%
14	Flucloxacillin	33,800	827,000.00	2.20%
15	Aminosidine	21,392	597,381.60	1.59%
16	Metronidazole	16,699	596,159.00	1.59%
17	Azithromycin	4,292	451,280.00	1.20%
18	Cefepime	1,070	300,040.00	0.80%
19	Polymixin	110	275,000.00	0.73%
20	Imipenem/cilastatin	200	243,000.00	0.65%
21	Phenoxymethylpenicillin	100,000	210,000.00	0.56%
22	Colistin	40	88,000.00	0.23%
23	Doxycycline	5,500	77,850.00	0.21%
24	Levofloxacin	200	72,000.00	0.19%
25	Dapsone	1,000	15,000.00	0.04%
	Totals for antibacterials ***(25, 73.5%)***	**443,981**	**35,615,498.60**	**94.86%**

Antiparasitic agents				
26	Sodium stibogluconate	5	64,435.50	0.17%
27	Albendazole	1,000	62,000.00	0.17%
28	Secnidazole	400	21,800.00	0.06%
29	Proguanil	67	404.00	0.00%
	Total antiparasitics **(4, 11.8%)**	**1472**	**148,639.50**	**0.40%**
Antifungal agents				
30	Fluconazole	10,800	1,063,980.00	2.83%
31	Itraconazole	6,000	270,000.00	0.72%
32	Griseofulvin	50,000	90,000.00	0.24%
33	Amphotericin B	200	70,000.00	0.19%
	Total antifungals **(4, 11.8%)**	**67000**	**1,493,980.00**	**3.98%**
Antiviral agents				
34	Acyclovir	5,800	285,025.00	0.76%
	Total antivirals **(1, 2.9%)**	**5,800.00**	**285,025.00**	**0.76%**
	TOTAL FOR ALL ANTIMICROBIALS (34, 100%)	**518,253.00**	**37,543,143.10**	***100%***

Table H4: Antimicrobial agents prescribed according to Kenya Essential Medicines List (2016) (Indicator 8)

No.	Antimicrobial name	Frequency (n, %)	On KEML 2016
Antibacterial agents			
1	Amikacin	2 (0%)	Yes
3	Amoxicillin/clavulanic acid	13 (1%)	Yes
4	Azithromycin	103 (12%)	Yes
5	Cefazolin	2 (0%)	Yes
6	Cefepime	35 (4%)	No
7	Cefixime	1 (0%)	Yes
8	Ceftazidime	1 (0%)	Yes
9	Ceftriaxone	298 (33%)	Yes
10	Cefuroxime	9 (1%)	Yes
11	Ciprofloxacin	28 (3%)	Yes
12	Clarithromycin	1 (0%)	Yes
13	Clindamycin	12 (1%)	Yes
14	Doxycycline	4 (0%)	Yes
15	Flucloxacillin	23 (3%)	Yes
16	H. pylori kit	2 (0%)	Yes
17	Imipenem/cilastatin	1 (0%)	Yes
18	Levofloxacin	28 (3%)	Yes
19	Linezolid	10 (1%)	Yes
20	Meropenem	30 (3%)	No
21	Metronidazole	87 (10%)	Yes
22	Nitrofurantoin	4 (0%)	Yes
23	Piperacillin/tazobactam	14 (2%)	No
24	Sulphamethoxazole/trimethoprim	12 (1%)	Yes
25	Vancomycin	38 (4%)	Yes
Antiparasitic agents			

26	Albendazole	4 (0%)	Yes
27	Artemether/lumefantrine	9 (1%)	Yes
28	Artesunate	13 (1%)	Yes
2	Paromomycin	11 (1%)	Yes
29	Proguanil	2 (0%)	Yes
Antifungal agents			
30	Amphotericin B	8 (1%)	Yes
31	Fluconazole	59 (7%)	Yes
32	Griseofulvin	1 (0%)	Yes
33	Itraconazole	1 (0%)	No
Antiviral agents			
34	Acyclovir	28 (3%)	Yes
	TOTAL	**894 (100%)**	**Yes-814 (91.1%)**
			No-80 (8.9%)

Table H5: Cost of prescribed antimicrobial agents for the study population (Indicator 9)

	Antimicrobial agent	Frequency	Route of administration	Doses prescribed	Unit cost (KShs.)	Cost of prescribed treatment (KShs.)	Percentage cost
	Antibacterial agents						
1	Amikacin	2	Parenteral	11	502	5522	0.2%
2	Amoxicillin/Clavulanic acid	13	Oral	146	20	2920	0.1%
3	Azithromycin	103	Oral	363	10	3630	0.2%
4	Cefazolin	2	Parenteral	24	176	4224	0.2%
5	Cefepime	35	Parenteral	681	169	115089	5.1%
6	Cefixime	1	Oral	5	18	90	0.0%
7	Ceftazidime	1	Parenteral	10	160	1600	0.1%
8	Ceftriaxone	294	Parenteral	3766	75	282450	12.5%
	Ceftriaxone (Rocephine)	4	Parenteral	42	1107	46494	2.1%
9	Cefuroxime	6	Parenteral	75	130	9750	0.4%
	Cefuroxime	3	Oral	20	18	360	0.0%
10	Ciprofloxacin	24	Oral	433	3	1299	0.1%
	Ciprofloxacin	4	Parenteral	32	556	17792	0.8%
11	Clarithromycin	1	Oral	6	21	126	0.0%
12	Clindamycin	6	Parenteral	140	108	15120	0.7%
	Clindamycin	6	Oral	183	7	1281	0.1%
13	Doxycyline	4	Oral	46	2	92	0.0%
14	Flucloxacillin	17	Parenteral	478	140	66920	3.0%
	Flucloxacillin	6	Oral	121	6	726	0.0%
15	*H.pylori* kit	2	Oral	12	306	3672	0.2%
16	Imipenem/Cilastatin	1	Parenteral	6	475	2850	0.1%
17	Levofloxacin	14	Parenteral	56	220	12320	0.5%
	Levofloxacin	14	Oral	99	30	2970	0.1%
18	Linezolid	10	Parenteral	176	1102	193952	8.6%
19	Meropenem	30	Parenteral	477	915	436455	19.3%
20	Metronidazole	72	Parenteral	1343	21	28203	1.2%
	Metronidazole	15	Oral	272	1	272	0.0%
21	Nitrofurantoin	4	Oral	98	2	196	0.0%
22	Piperacillin/tazobactam	14	Parenteral	536	800	428800	19.0%
23	Sulphamethoxazole/trimethoprim	12	Oral	254	2	508	0.0%
24	Vancomycin	38	Parenteral	588	703	413364	18.3%
	Antiparasitic agents						
25	Albendazole	4	Oral	15	2	30	0.0%
26	Artemether/Lumefantrine	9	Oral	46	12	552	0.0%
27	Artesunate	13	Parenteral	73	192	14016	0.6%
28	Paromomycin	11	Oral	341	20	6820	0.3%
29	Proguanil	2	Oral	37	6	222	0.0%

	Antifungal agents						
30	Amphotericin B	8	Parenteral	105	245	25725	1.1%
31	Fluconazole	7	Parenteral	72	110	7920	0.4%
	Fluconazole	52	Oral	594	77	45738	2.0%
32	Griseofulvin	1	Oral	8	6	48	0.0%
33	Itraconazole	1	Oral	15	45	675	0.0%
	Antiviral agents						
34	Acyclovir	25	Oral	984	7	6888	0.3%
	Acyclovir	3	Parenteral	84	585	49140	2.2%
	TOTALS	**894**		**12,873**		**2,256,821/=**	**100.0%**

Table H6: Duration of prescribed antimicrobial treatment for specific antimicrobial agents (Indicator 10)

	Antimicrobial agent	Frequency	Days of treatment		
			Total days	Average	Median
Antibacterial agents					
1	Amikacin	2	5	2.5	2.5
2	Amoxicillin/Clavulanic acid	13	80	6.15	5
3	Azithromycin	103	385	3.74	3
4	Cefazolin	2	8	4	4
5	Cefepime	35	260	7.43	6
6	Cefixime	1	5	5	5
7	Ceftazidime	1	2	2	2
8	Ceftriaxone	298	1958	6.57	6
9	Cefuroxime	9	40	4.44	5
10	Ciprofloxacin	28	239	8.54	6
11	Clarithromycin	1	3	3	3
12	Clindamycin	12	97	8.08	7
13	Doxycyline	4	29	7.25	7
14	Flucloxacillin	23	150	6.52	6
15	H.pylori kit	2	8	4	4
16	Imipenem/Cilastatin	1	2	2	2
17	Levofloxacin	28	132	4.71	4.5
18	Linezolid	10	84	8.4	9.5
19	Meropenem	30	211	7.03	6
20	Metronidazole	87	556	6.39	6
21	Nitrofurantoin	4	37	9.25	7.5
22	Piperacillin/tazobactam	14	161	11.5	10.5
23	Sulphamethoxazole/trimethoprim	12	86	7.17	4
24	Vancomycin	38	295	7.76	7.5

Antiparasitic agents					
25	Albendazole	4	9	2.25	1
26	Artemether/Lumefantrine	9	26	2.89	3
27	Artesunate	13	46	3.54	3
28	Paromomycin	11	75	6.82	5
29	Proguanil	2	37	18.5	18.5
Antifungal agents					
30	Amphotericin B	8	105	13.14	13.5
31	Fluconazole	59	622	10.54	8
32	Griseofulvin	1	4	4	4
33	Itraconazole	1	3	3	3
Antiviral agents					
34	Acyclovir	28	338	12.07	9.5
	TOTALS	**894**	**6098**	**6.82**	**5**

Table H7: Specific antimicrobial agents prescribed actually administered (Indicator 15)

	Antimicrobial agent	Frequency	Doses prescribed	Doses administered	Percentage
Antibacterial agents					
1	Amikacin	2	11	2	18.2%
2	Amoxicillin/Clavulanic acid	13	146	94	64.4%
3	Azithromycin	103	363	346	95.3%
4	Cefazolin	2	24	13	54.2%
5	Cefepime	35	681	368	54.0%
6	Cefixime	1	5	5	100.0%
7	Ceftazidime	1	10	2	20.0%
8	Ceftriaxone	298	3808	2780	73.0%
9	Cefuroxime	9	95	69	72.6%
10	Ciprofloxacin	28	465	359	77.2%
11	Clarithromycin	1	6	6	100.0%
12	Clindamycin	12	323	223	69.0%
13	Doxycyline	4	46	22	47.8%
14	Flucloxacillin	23	599	338	56.4%
15	H.pylori kit	2	12	14	116.7%
16	Imipenem/Cilastatin	1	6	3	50.0%
17	Levofloxacin	28	155	107	69.0%
18	Linezolid	10	176	115	65.3%
19	Meropenem	30	477	345	72.3%
20	Metronidazole	87	1615	1135	70.3%
21	Nitrofurantoin	4	98	35	35.7%
22	Piperacillin/tazobactam	14	536	304	56.7%

23	Sulphamethoxazole/trimethoprim	12	254	164	64.6%
24	Vancomycin	38	588	380	64.6%
Antifungal agents					
25	Amphotericin B	8	105	89	84.8%
26	Fluconazole	59	666	503	75.5%
27	Griseofulvin	1	8	3	37.5%
28	Itraconazole	1	15	7	46.7%
Antiparasitic agents					
29	Albendazole	4	15	10	66.7%
30	Artemether/Lumefantrine	9	46	29	63.0%
31	Artesunate	13	73	48	65.8%
32	Paromomycin	11	341	119	34.9%
33	Proguanil	2	37	28	75.7%
Antiviral agents					
34	Acyclovir	28	1068	598	56.0%
TOTALS		**894**	**12,873**	**8,663**	**67.3%**

Appendix I:IREC Approval

MU/MTRH-INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471/2/3

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET

Reference: IREC/2018/203
Approval Number: 0003189

22nd January, 2019

Dr. Moin Roselyne Kapkarich,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
22 JAN 2019
APPROVED
P.O. Box 4606-30100 ELDORET

Dear Dr. Kapkarich,

RE: FORMAL APPROVAL

The MU/MTRH- Institutional Research and Ethics Committee has reviewed your research proposal titled: -

"Pattern of Use of Antimicrobial Agents in the Adult Medical Wards at Moi Teaching and Referral Hospital, Eldoret, Kenya".

Your proposal has been granted a Formal Approval Number: ***FAN: IREC 3189*** on 22nd January, 2019. You are therefore permitted to begin your investigations.

Note that this approval is for 1 year; hence will expire on 21st January, 2020. If it is necessary to continue with this research beyond the expiry date, a request for continuation should be made in writing to IREC Secretariat two months prior to the expiry date. You will be required to submit progress report(s) on application for continuation, at the end of the study and any other times as may be recommended by the Committee.

Furthermore, you must notify the Committee of any proposal change (s) or amendment (s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. You will also be required to seek further clearance from any other regulatory body/authority that may be appropriate and applicable to the conduct of this study.

Sincerely,

DR. S. NYABERA
DEPUTY-CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc CEO - MTRH Dean - SOP Dean - SOM
Principal - CHS Dean - SON Dean - SOD

Appendix J: Hospital Approval (MTRH)

An ISO 9001:2015 Certified Hospital

MOI TEACHING AND REFERRAL HOSPITAL

Telephone :(+254)053-2033471/2/3/4
Mobile: 722-201277/0722-209795/0734-600461/0734-683361
Fax: 053-2061749
Email: ceo@mtrh.go.ke/directorsofficemtrh@gmail.com

Nandi Road
P.O. Box 3 – 30100
ELDORET, KENYA

Ref: ELD/MTRH/R&P/10/2/V.2/2010

23rd January, 2019

Dr. Moin Roselyne Kapkarich,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

APPROVAL TO CONDUCT RESEARCH AT MTRH

Upon obtaining approval from the Institutional Research and Ethics Committee (IREC) to conduct your research proposal titled:-

"Pattern of Use of Antimicrobial Agents in the Adult Medical Wards at Moi Teaching and Referral Hospital, Eldoret, Kenya".

You are hereby permitted to commence your investigation at Moi Teaching and Referral Hospital.

MOI TEACHING AND REFERRAL HOSPITA.
CEO
APPROVED
23 JAN 2019
SIGN.....
100, ELDORE

23/01/2019
DR. WILSON K. ARUASA, *MBS*
CHIEF EXECUTIVE OFFICER
MOI TEACHING AND REFERRAL HOSPITAL

cc - Senior Director, (CS)
- Director of Nursing Services (DNS)
- HOD, HRISM