PREVALENCE AND DETERMINANTS OF ANTIBIOTIC PRESCRIPTION AMONG CHILDREN ADMITTED TO TWELVE PUBLIC HOSPITALS IN KENYA

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A DISSERTATION SUBMITTED TO THE DEPARTMENT OF PUBLIC AND GLOBAL HEALTH IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE AWARD OF THE DEGREE OF MASTER OF PUBLIC HEALTH OF THE UNIVERSITY OF NAIROBI

UNIVERSITY OF NAIROBI

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DEDICATION

I dedicate this dissertation to my friends, Clare who taught me that anything is possible under the sun, Robert who pushed me to be my best self, Lydia who constantly reminded me of my capabilities and my siblings and parents for their emotional and financial support.

ACKNOWLEDGEMENTS

First and foremost, to my supervisors, **Dr. Michuki Maina**, **Dr. Samuel Akech** and **Dr. Marshal Mweu** for the dedicated and kind guidance they provided throughout my time as their student. I am deeply grateful for their mentorship and the research skills they fostered in me.

I am also thankful to KEMRI-Wellcome Trust (KWTRP) and Initiative to Develop African Research Leaders (IDeAL) for the scholarship they awarded me to carry out this project. Special thanks to the Health Services Unit, specifically the child Severe Febrille Illness (cSEFI) team for hosting me, Paul Mwaniki and Morris Ogero for their statistical guidance.

I owe my sincere gratitude to the Clinical Information Network's data clerks and data managers for collection, entry and ensuring the accuracy of the data used in this study. Finally, to God Almighty for making all this possible.

This work was supported through the DELTAS Africa Initiative [DEL-15-003]. The DELTAS Africa Initiative is an independent funding scheme of the African Academy of Sciences (AAS)'s Alliance for Accelerating Excellence in Science in Africa (AESA) and supported by the New Partnership for Africa's Development Planning and Coordinating Agency (NEPAD Agency) with funding from the Wellcome Trust [107769/Z/10/Z] and the UK government. The views expressed in this dissertation are those of the author(s) and not necessarily those of AAS, NEPAD Agency, Wellcome Trust or the UK government.

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LIST OF ABBREVIATIONS/ACRONYMS

ATC	Anatomical Therapeutic Chemical
CIN	Clinical Information Network
HICs	High Income Countries
IDeAL	Initiative to Develop African Research Leaders
IPC	Infection Prevention and Control
KPA	Kenya Paediatric Association
KWTRP	KEMRI-Wellcome Trust Research Program
LMICs	Low-and Middle-Income Countries
MoH	Ministry of Health
PAR	Paediatric Admission Record
REDCap	Research Electronic Data Capture
WHO	World Health Organization

DEFINITION OF OPERATIONAL TERMS

Antibiotic - An antimicrobial agent with the ability to kill or inhibit bacterial growth

Antimicrobial/Antibiotic resistance – "Microorganisms such as bacteria, fungi, viruses and parasites change when exposed to antimicrobial drugs such as antibiotics, antifungals, antivirals, antimalarials and anthelmintics and as a result, the medicines become ineffective"

Antibiotic stewardship - A set of actions at the individual, national and global level, and across animal, human and environmental health which promote the responsible use of antibiotics

Judicious use - of antibiotics is the use of antibiotics for the right condition and right patient for the right duration.

Broad-spectrum antibiotic - An antibiotic that works against a wide range of gram-positive and gram-negative bacteria

Empiric treatment - The choice of antibiotics by clinicians based on their clinical judgement and expertise in the absence of laboratory data and other information

Injudicious use - of antibiotics where they are not indicated or for non-therapeutic reasons

Paediatric patients – Children aged above one month

ABSTRACT

Background- At least one antibiotic is given to 60% of children throughout their hospital stay, with broad-spectrum penicillins being the most prescribed worldwide. Injudicious antibiotic use in children's hospitals has led to the emergence and transmission of antibiotic resistance, death, prolonged hospitalization, adverse drug events and increased treatment costs. So far, there are few studies carried out on the factors influencing prescription of antibiotics among hospitalized children in Sub-Saharan Africa. There is therefore an urgency to understand these factors in order to strengthen antibiotic stewardship programs in hospitals.

Objectives- This study described the antibiotic prescription patterns and identified the determinants of antibiotic prescription among children admitted to hospitals in the Clinical Information Network (CIN) in Kenya.

Methods- This was a cross-sectional analytic study carried out in 12 hospitals that are part of CIN across 11 counties in Kenya. Children older than two months and admitted in paediatric wards in CIN hospitals from 2014 to 2020 were included in the study. Patients with missing information on treatment were excluded. Data collected from hospital records were exported from REDCap and saved in an Excel spreadsheet. Both descriptive and inferential analyses were done using R software, version 4.1.2. Antibiotic prescription, a binary variable was the outcome of interest. Univariable and multivariable mixed-effects logistic regression were performed with the variable hospital added as a random effect to identify the determinants of antibiotic prescription.

Results- The estimated period prevalence of antibiotic prescription between 2014 and 2020 was 81.1% (95% CI: 80.9 - 81.3%). Penicillins (42.6%), aminoglycosides (26.6%) and cephalosporins (19.6%) were the commonly prescribed classes of antibiotics among children admitted to the CIN hospitals. From the multivariable analysis, age (OR 0.8), duration of hospital stay (ORs 4.7;

medium duration, 7.5; long duration) and diagnoses (ORs 162.0; pneumonia, 29.2; meningitis, 1.3; diarrhoea, 1.3; dehydration, 12.1; malnutrition) were found to be determinants of antibiotic prescription.

Conclusion- The prevalence of antibiotic prescription was high, reflecting high usage of antibiotics in paediatric wards in public Kenyan hospitals. Age, duration of hospital stay and diagnoses were shown to influence the prescription of antibiotics among children.

Recommendations- The clinicians should be trained on judicious antibiotic use , diagnostic support improved and strategies to ensure adherence to treatment guidelines adopted in the hospitals.

CHAPTER ONE: INTRODUCTION

1.0 Introduction

This chapter outlines the background, problem statement and justification of the study. Additionally, the study's research question and objectives are included.

1.1 Background

Antibiotics are more frequently prescribed to children given that infectious diseases are generally more common among children compared to adults (Hsia et al., 2019). Globally, the number of antibiotics consumed by children increased from 16.6 to 17.8 billion standard units between 2011 and 2015 (Jackson C. et al., 2019). Antibiotic consumption among children in High Income Countries (HICs) however reduced during this period, indicating an outstanding increase in Low- and Middle-Income countries (LMICs) (Klein et al., 2018). A child in a LMIC receives an average of 24.5 antibiotic prescriptions from birth up to the age of 5 years which is noteworthy as two antibiotic prescriptions in a year is treated as excessive in HICs (Vaz et al., 2014, Fink et al., 2019). Some studies have shown that at least one antibiotic is given to 60% of children throughout their hospital stay, with the prevalence of antibiotic use among hospitalized children in Sub-Saharan Africa ranging from 63.3% to 86.6% (Gerber et al., 2010, Sviestina and Mozgis, 2014).

The most widely prescribed class of antibiotics are the broad-spectrum penicillins, whose consumption rates increased by 36% during the last decade (Klein et al., 2018). Moreover, there has been a notable increase in the consumption of cephalosporins globally due to an enhanced access to antibiotics as a result of economic growth and increased healthcare expenditure (Thomas P Van Boeckel et al., 2014). A number of studies in both HICs and LMICs have shown that cephalosporins, aminoglycosides, penicillins, nitroimidazole derivatives, macrolides and fluoroquinolones are frequently prescribed for paediatric inpatients (Zhang et al., 2018, Sharma et al., 2015, Labi et al., 2018, Versporten et al., 2018, Wang et al., 2021, Sviestina and Mozgis, 2014, Sviestina and Mozgis, 2018). In Kenya, the most prescribed are cephalosporins, aminoglycosides and penicillins, with ceftriaxone being the most prescribed cephalosporin (Momanyi et al., 2019, Maina et al., 2020, Okoth et al., 2018, Nicholas C. Mulwa et al., 2015). In addition, the combination of gentamicin and benzylpenicillin, which is the recommended primary treatment for most acute paediatric infections in Kenya, is often used in paediatric medical wards (Maina et al., 2020).

Among children, the indications for antibiotic prescription are lower respiratory tract infections, fever and skin and soft tissue infections. (Hariharan et al., 2009, Alakhali and Mohammad, 2014, D. Curcio et al., 2009). In Sub-Saharan Africa, respiratory infections and diarrhoea are the most common diagnoses for antibiotic use among children under the age of five years (Fink et al., 2019). Similar findings have been reported in Kenya where the most recurrent diagnosis among children warranting antibiotic prescription are lower respiratory tract infections (Maina et al., 2020).

Judicious use of antibiotics involves prescribing the right dose, at the accurate frequency, for an appropriate period, through the right route of administration and at a cost a patient can afford (Obakiro et al., 2021). Up to 60% of antibiotics are prescribed injudiciously in children's hospitals (Sviestina and Mozgis, 2018). This includes prescriptions for unindicated conditions, use of broad-spectrum rather than narrow-spectrum antibiotics, parenteral rather than oral antibiotics where they would be effective and antibiotic prescription for viral infections(Gerber et al., 2015, Sharma et al., 2015). In Sub-Saharan Africa where infection rates are much higher, antibiotic availability is limited and drug use is poorly regulated, there is a remarkable extent of irrational antibiotic use (Umar et al., 2018). This has contributed to the development and continual transmission of antibiotic resistance, which has in turn led to increased risk of death, prolonged hospitalization, increased treatment costs, and delayed healing (Ahmed et al., 2018, Skender et al., 2021).

Determinants of antibiotic prescription can be grouped into patient characteristics, hospital-level factors, underlying community epidemiology and national level factors. Patient characteristics are mainly clinical and demographic while underlying community epidemiology include seasonality and location of health centres (Brembilla et al., 2016). Hospital-level factors include the level of training of health workers, their cadres, availability of drugs and diagnostic capacities (Means et al., 2014, Mekuria et al., 2019, Obakiro et al., 2021). Ultimately, the national-level factors are guidelines and policies on antibiotic use (Obakiro et al., 2021). The factors reported to influence patterns of antibiotic use among children in Sub-Saharan Africa are cultural preferences, the child's sex, mother's level of education, nutritional status, sanitation, comorbidities and the severity of clinical symptoms (Monteiro et al., 2017, Means et al., 2014, Rogawski et al., 2017)

In Kenya, age, social class, examination, negative malaria test, seasonal variation and primary diagnosis influence antibiotic prescription among paediatric outpatients (Hooft et al., 2021). Pressure from patients, the desire to stock out near expiring drugs, lack of treatment guidelines in hospitals, level of training of a clinician and health insurance cover of a patient also determine the type of antibiotic prescribed (Mekuria et al., 2019, McKnight et al., 2019). There is however limited evidence on the determinants of antibiotic prescription among hospitalized children.

1.2 Statement of the research problem

One of the most significant developments in modern medicine is antibiotic therapy which has reduced morbidity and mortality in children over the years (Ventola, 2015). The injudicious use of antibiotics has however occasioned the emergence and increasing transmission of antibiotic resistance, bringing about an increased threat from infections (Friedman et al., 2016, Brogan et al., 2018). Antibiotic resistance is expected to cause up to 10 million deaths worldwide per year by 2050 (Skender et al., 2021). In Sub-Saharan Africa, antibiotic resistance caused close to 1.07 million deaths in 2019, with the leading resistant strains of bacteria being *Streptococcus pneumoniae* and *Klebsiella pneumoniae* (Murray et al., 2022). Another consequence of injudicious use of antibiotics is an increase in the risk of adverse drug reactions (Okoth et al., 2018).

There are concerns of injudicious use of antibiotics in Kenya, particularly among inpatients whose prevalence of antibiotic use is estimated at 82% (Okoth et al., 2018). A majority of children are given empiric antibiotic therapies, in particular, less than 0.3% of those admitted in paediatric medical wards receive treatments based on antibiotic susceptibility tests (Maina et al., 2020). Prescription using proprietary names, especially for combination drugs is also common in Kenyan hospitals as a result of the influence by medical representatives who promote drugs in these settings (Nicholas C. Mulwa et al., 2015, McKnight et al., 2019). There are also reports of considerable prescription of broad-spectrum antibiotics, over-prescription and extended durations of treatment which contribute to the development of antibiotic resistance (Momanyi et al., 2019, Nicholas C. Mulwa et al., 2015, Tank et al., 2019). In addition, children with a primary diagnosis of viral disease are often prescribed antibiotics, while other children are under-prescribed antibiotics due to unavailability of drugs in hospitals (Rhee et al., 2019, Hooft et al., 2021).

Infectious diseases are one of the leading causes of under-five deaths in Kenya, which calls for the appropriate use of antibiotics in order to reduce deaths from bacterial infections (Sharrow et al., 2022). Baseline data on prescription patterns and their determinants are therefore required to improve antibiotic prescription among paediatrics and to develop strategies to strengthen antibiotic stewardship programs in Kenyan hospitals.

1.3 Justification of the study

There is a dearth of studies in Kenya carried out on the determinants of antibiotic prescription among hospitalized children. The few available studies only focus on the factors influencing antibiotic prescription among outpatient paediatrics presenting with undifferentiated febrile illness and acute respiratory tract infections (Mekuria et al., 2019, Hooft et al., 2021). There is therefore still a gap in understanding the drivers of antibiotic prescription among admitted children. It is expected that the findings of this study will inform existing guidelines on antibiotic use by identifying areas of improvement which will in the long run sustain antibiotic stewardship programs in Kenyan hospitals.

1.4 Research questions

1. What is the prevalence of antibiotic use among children admitted to hospitals in Kenya?

2.What characteristics are associated with antibiotic prescriptions in children admitted to hospitals in Kenya?

1.5 Objectives

1.5.1 Broad Objective

To describe the antibiotic prescription patterns and identify the determinants of antibiotic prescription among children admitted to hospitals in the Clinical Information Network (CIN) in Kenya.

1.5.2 Specific Objectives

1. To describe the demographic and clinical characteristics of children receiving antibiotic prescriptions in the study hospitals
2. To estimate the period prevalence of antibiotic use among children admitted to CIN hospitals between 2013 and 2020
3. To establish the commonly used classes of antibiotics in the study hospitals
4. To identify the determinants of antibiotic prescription among children admitted to the study hospitals.

CHAPTER TWO: LITERATURE REVIEW

2.0 Introduction

This chapter summarizes literature on antibiotic prescription among children in both LMICs and HICs. It mainly focuses on the prevalence of antibiotic prescription among children, classes of antibiotics commonly prescribed, characteristics of children receiving antibiotics, determinants of antibiotic prescription and the consequences of injudicious antibiotic use.

2.1 Prevalence of antibiotic use among children

The prevalence of antibiotic use remains high especially for paediatric patients. Among children in non-European countries, the prevalence of antibiotic use was 43.8% while that of children in European countries was 39.4% in 2011(Versporten et al., 2013). Recent reports have however shown that there has been a continual 36% surge in the use of antibiotics in the past ten years worldwide (Momanyi et al., 2019). In North America, 35% of hospitalized children receive at least one antibiotic during their stay at the hospital (Tribble et al., 2020). Comparably, the prevalence of antimicrobial use in the United Kingdom is 41% in paediatric specialist hospitals and 32% in acute hospitals (Gibbons et al., 2019). Among Asian countries, the prevalence of antibiotic use is approximately 64% for outpatients and 83% for inpatients in China, 77.6% in Pakistan, 31% in Japan and 20% in Korea (Guo et al., 2021, Saleem et al., 2019, Ruth Brauer et al., 2019). In Sub-Saharan Africa, the prevalence of antibiotic use among children ranges from 70.6% to 98% (Labi et al., 2018, Fadare et al., 2015, Monteiro et al., 2017, Gizework and Seyfe, 2015).

2.2.0 Commonly used classes of antibiotics among children

2.2.1 Anatomical Therapeutic Chemical Classification

The World Health Organization's (WHO) approved Anatomical Therapeutic Chemical (ATC) categorization system is currently the most universally accepted classification system for antibiotics(Chen et al., 2012). It classifies antibiotics into distinct groups based on the organ or system on which they act, as well as their therapeutic and chemical properties(Chen et al., 2012). These groups are;

2.2.1.1 Penicillins

The most widely used class of antibiotics worldwide are the broad-spectrum penicillins (Klein et al., 2018). In the United States, penicillins are among the chiefly prescribed antibiotics for children diagnosed with pneumonia, accounting for approximately 14% of antibiotic prescriptions (Kronman et al., 2011). Similarly, penicillins are widely used in paediatric wards in Germany and Italy (Araujo da Silva et al., 2020, Buccellato et al., 2015). Between 2004 and 2011, the use of broad-spectrum penicillins reduced while that of penicillins with beta-lactamase inhibitors increased in Italy (Buccellato et al., 2015). The use of penicillins is similarly common in LMICs including Nepal, Bangladesh, Ghana and Nigeria (Boone et al., 2021, Amponsah et al., 2021, Nepal et al., 2020, Umar et al., 2018). Studies have shown that amoxicillin is the most prescribed of all the penicillins (Hsia et al., 2019, Nepal et al., 2020). The highest percentage of antibiotics prescribed for inpatients in Hong Kong nonetheless is amoxiclav (Chui et al., 2020).

2.2.1.2 Cephalosporins

Second to broad-spectrum penicillins are the cephalosporins (Klein et al., 2018). Third generation cephalosporins are the most widely used of all the cephalosporins (Thomas P Van Boeckel et al., 2014). Their consumption has increased over the last decade owing to their favourable frequency of administration which promotes lower costs of drugs and can also be easily administered by understaffed health facilities (Thomas P Van Boeckel et al., 2014). Third generation cephalosporins are often prescribed for community acquired infections (Ciofi Degli Atti et al., 2019). They are the most used antibiotics in China, Saudi Arabia and Nepal (Guo et al., 2021, Kazzaz et al., 2020, Nepal et al., 2020). Notably, ceftriaxone is the most frequently prescribed antibiotic among the third generation cephalosporins in Africa, the Eastern Mediterranean, Europe, and Southeast Asia (Yingfen Hsia and networks, 2019).

2.2.1.3 Aminoglycosides

Aminoglycosides are among the top three prescribed classes of antibiotics among children in HICs (Osowicki et al., 2014, De Luca et al., 2016). In Brazil, it is the chiefly prescribed in neonatal intensive care units. Similar findings were reported in Sub-Saharan Africa where aminoglycosides are among the mainly prescribed antibiotics for community acquired infections among paediatric inpatients (Labi et al., 2018).

Other commonly used classes of antibiotics globally are quinolones and macrolides (Klein et al., 2018). In the United States however, sulfamethoxazole and trimethoprim derivatives are the most used class of antibiotics (Tribble et al., 2020). Of concern is the notable rise in the use of last resort antibiotic classes like carbapenems and polymyxins between the years 2000 and 2015, particularly in LMICs (Klein et al., 2018). A study revealed that carbapenems are mostly prescribed for hospital acquired infections (Ciofi Degli Atti et al., 2019).

2.2.2 Access, Watch and Reserve classification system

Antibiotics in the essential medicines list for children were grouped into three main categories by the WHO in 2017 (Table 1). These are the access, watch and reserve groups also known as AWARe (Yingfen Hsia and networks, 2019). The access group contains antibiotics with a narrow spectrum which are usually approved as first and second line drugs for common clinical infections (Sharland et al., 2018). The watch group consists of classes of antibiotics with a broader spectrum which correspond to the agents with the highest priority on the list of antibacterial medications that are crucial for human medicine (Sharland et al., 2018). Finally, the reserve group comprises last-resort antibiotics which are mostly used to treat multidrug-resistant bacteria infections (Sharland et al., 2018). These groups are coded using traffic light colours with access coded as green, watch coded as amber and reserve coded as red (Yingfen Hsia and networks, 2019).

Table 1: AWaRe classification of antibiotics

Class	**Antibiotics**
Access	Amikacin Amoxicillin Amoxiclav Ampicillin Azithromycin Benzylpenicillin Cefalexin Cefadroxil Clindamycin Doxycycline Flucloxacillin Gentamicin Metronidazole Nitrofurantoin

	Tinidazole Chloramphenicol
Watch	Ceftazidime Ceftriaxone Cefixime Ciprofloxacin Clarithromycin Cefaclor Cefotaxime Cefuroxime Cefepime Cefpodoxime Lanomycin Streptomycin Erythromycin Sulfamethoxazole +Trimethoprim Piperacillin + Tazobactam
Reserve	Meropenem Vancomycin

A global study on antibiotic use by children showed that all countries prescribed the reserve antibiotics least, with Mexico having the highest proportion (Yingfen Hsia and networks, 2019). Slovenia appeared to use the access antibiotics the most while China had the highest percentage of watch antibiotics, with Guinea having no report of watch antibiotics use (Yingfen Hsia and networks, 2019). Fourth generation cephalosporins are generally the most common reserve antibiotics used with cefepime mainly being prescribed for lower respiratory tract infections (Yingfen Hsia and networks, 2019). In Tanzania, the most prescribed antibiotics belong to the access group whereas hospitals in Uganda prescribe watch antibiotics the most with ceftriaxone accounting for the highest percentage (Jeremiah Seni 2020, Kiggundu et al., 2022).

2.2.3 Common combination drugs

Some antibiotics are prescribed as combination drugs. For instance, in Italy and China, approximately 41% of children receive a combination of two or more antibiotics, which are mostly prescribed with antituberculosis drugs (Guo et al., 2021, Zhang et al., 2018, Tersigni et al., 2019). Combinations of metronidazole and ampicillin, cefuroxime and gentamicin, metronidazole and ceftriaxone or amoxicillin, benzylpenicillin and clindamycin are given to paediatric inpatients in Latvia (Sviestina and Mozgis, 2014). In Ethiopia, the most common combination is ceftriaxone and amoxicillin, while ampicillin and ciprofloxacin are prescribed the least (Yehualaw et al., 2021). A study in Nigeria revealed that ampicillin and cloxacillin was the most frequently prescribed combination for hospitalized children (Umar et al., 2018).

2.3 Route of administration of antibiotics

Antibiotics are mainly prescribed either orally or parenterally (Kate McCarthy, 2020). Oral antibiotics are appropriate in treating bacterial infections in hospitals, but patients are often given antibiotics parenterally in cases where oral antibiotics could work (Kate McCarthy, 2020).

Parenteral antibiotics are recommended as initial treatment for life-threatening infections. Studies in both HICs and LMICs have shown that a majority of hospitalized children are given antibiotics parenterally (Quaak et al., 2018, Kebede et al., 2017, Umar et al., 2018, Gharbi et al., 2016, Labi et al., 2018, Wang et al., 2021). In Switzerland however, most of the antimicrobials were administered orally to hospitalized patients with around 7% of intravenous antibiotics being switched to oral (Zingg et al., 2019). Similarly, a majority of hospitalized children in Italy were administered antibiotics orally (Buccellato et al., 2015). There are also trends of switching route of administration, for instance, 20.3% of admitted children in Hong Kong had their antibiotics switched from parenteral to oral (Chui et al., 2020).

Compared to inpatients, a majority of outpatient paediatrics receive oral antibiotics as their infections are not severe (Kate McCarthy, 2020). A study in the United States showed that parenteral antibiotics were administered to only 1.8% of children in the outpatient department (Howard et al., 2020).

2.4 Demographic characteristics of children receiving antibiotic prescriptions

Studies have described antibiotic use among children in terms of demographic factors like age, sex and economic status. Younger children have a higher percentage of antibiotic use compared to older ones, for instance, the median age of children receiving antibiotic prescriptions in North America is 3.8 years (Tribble et al., 2020). Similarly, the highest proportion of antibiotic prescription was among the youngest age category of less than two years in Asian countries (Ruth Brauer et al., 2019). In Hong Kong, however, there is an increased prescription of antibiotics between ages five to nine years (Chui et al., 2020). Children in Italy also receive more antibiotics compared to neonates (Piovani et al., 2014). In Sub-Saharan Africa, children aged between one month and five years receive more antibiotic prescriptions compared to other age groups (Monteiro et al., 2017, Umar et al., 2018, Labi et al., 2018, Obura et al., 2021).

The percentage of male children receiving antibiotics has been reported to be higher than females, case in point, a study done in the United States revealed than a higher percentage of males received antibiotic prescriptions compared to females (Tribble et al., 2020). Similarly, more males than females receive antibiotics in India (Hafeez et al., 2020). Similar findings were reported in Ethiopia where a higher proportion of males received antibiotics compared to females (Yehualaw et al., 2021). In Italy, however, antibiotic prescription is similar between males and females.

In terms of economic status, children admitted to non-European wards are likely to receive more antibiotics than children admitted to European wards (Versporten et al., 2013). Furthermore, residents with an averagely lower income have a higher prevalence of antibiotic use compared to those with high income (Piovani et al., 2014).

2.5 Clinical characteristics of children receiving antibiotic prescriptions

Antibiotics are given to paediatric inpatients for both therapeutic and prophylactic reasons. (Tribble et al., 2020) medical prophylaxis, and surgical prophylaxis (Yingfen Hsia and networks, 2019). In North America, antibiotics are mostly prescribed for the treatment of lower respiratory tract infections among inpatient paediatrics (J.E Fischer, 2000, Tribble et al., 2020). Within Asian countries, antibiotics are also mainly prescribed for therapeutic purposes among children diagnosed with lower respiratory tract infections, soft tissue infections and sepsis (Boone et al., 2021, Gandra et al., 2017, Xu et al., 2020, Limato et al., 2021). Similarly, sepsis was found to be the most common indication for antimicrobial prescription in Australia (McMullan et al., 2020).

In Africa, antibiotics are often given for community acquired infections, followed by medical and surgical prophylaxis, with hospital acquired infections having the least percentage (Jeremiah Seni 2020). A study carried out in Sub-Saharan Africa revealed that the leading diagnoses for antibiotic prescription among sick children visiting health facilities were respiratory illnesses, diarrhoea and malaria (Fink et al., 2019). Correspondingly, a study in Uganda found that up to 42% of patients who were suffering from malaria and did not have a clinical indication for antibiotic treatment received antibiotics (Means et al., 2014). In Kenya, up to 55% of children diagnosed with malaria received antibiotic prescriptions (Hooft et al., 2021).

Among outpatients, those receiving antibiotic prescriptions are mainly diagnosed with upper respiratory tract infections, gastroenteritis and urinary tract infections (Al-Niemat et al., 2014). Other studies looking at outpatient paediatrics have however shown that lower respiratory tract infections are the main diagnoses for antibiotic prescription (Sie et al., 2021, Wushouer et al., 2021). Other clinical characteristics of children receiving antibiotics include fever, length of illness, examination and comorbidities (Hooft et al., 2021, Means et al., 2014, Yehualaw et al., 2021)

2.6.0 Determinants of antibiotic use among children

A number of patient-level and hospital-level factors have been identified as determinants of antibiotic prescription among paediatric patients.

2.6.1 Patient-level factors

These include age, sex, comorbidities, patient history, presenting symptoms, laboratory findings, primary diagnosis and duration of hospital stay.

2.6.1.1 Age

Antibiotic prescribing is associated with age group for a varying range of illnesses. In a recent study in Uganda, age group was found to be significantly associated with antibiotic prescription after adjusting for sex and disease severity (Obura et al., 2021). A similar study in Mozambique investigating the determinants of antibiotic prescription among children also revealed that age is associated with antibiotic use with an odds ratio of 5.496 (Monteiro et al., 2017). Additionally, in Nepal, patients younger than five years are more likely to be given antibiotics (Nepal et al., 2020). Other studies however found that patients in older age groups, three to twelve years, are more likely to be prescribed antibiotics (Ciofi Degli Atti et al., 2019).

Being young has been found to be related with low adherence to prescribed antibiotics (Zanichelli et al., 2019). A study in the United States, however, found that age was not associated with suboptimal antibiotic use (Tribble et al., 2020). Elsewhere, children less than the age of two years are given approximately 1.8 times more antibiotics than those aged above two years (Jeremiah Seni 2020). Something to note is that older children are more likely to be given inappropriate antibiotics as the prescriber might consider them as adults (Yehualaw et al., 2021).

2.6.1.2 Sex

Male children, irrespective of their age, have a higher likelihood of receiving antibiotic prescriptions as revealed in studies in Nepal and Tanzania (Jeremiah Seni 2020, Nepal et al., 2020). A study in South Africa revealed that male gender, whose interaction with pneumonia severity was found to be significant, increases the odds of getting a ceftriaxone prescription (Xaba et al., 2014). Being male is also associated with low adherence to antibiotic prescriptions (Zanichelli et al., 2019).

2.6.1.3 Comorbidities

A global PPS revealed that underlying diseases increased the odds of antibiotic prescription among paediatric patients (Bielicki et al., 2018). Another study also found that children with comorbidities such as asthma and obesity had higher odds of receiving more antibiotics (McGurn et al., 2021). In Uganda, the odds of inappropriate antibiotic prescription were lower if a patient was HIV positive (Means et al., 2014). The specific comorbidities in children associated with antibiotic use are however not mentioned in these studies (Bielicki et al., 2018, D'Amore et al., 2021).

2.6.1.4 Patient history

A study in Bangladesh found that patients who had used antimicrobials before admission were more likely to be given antimicrobials(Ahmed et al., 2018). Low breastfeeding scores, previous use of paracetamol, no vomiting in the past twenty-four hours, previous admissions and frequent hospital visits are also associated with antibiotic prescription (Rebnord et al., 2017, Jeremiah Seni 2020, Mekuria et al., 2019, Brembilla et al., 2016). In Kenya, children who present earlier in the course of their illness have higher odds of antibiotic prescription (Hooft et al., 2021).

2.6.1.5 Presenting symptoms

Paediatric patients presenting with fever have a higher likelihood of getting antibiotic prescriptions compared to those without (Ahmed et al., 2018, Covino et al., 2022). Other factors like clinical manifestation of infection at admission, gastrointestinal symptoms, lower and upper respiratory symptoms also determine whether antibiotics are prescribed for children (Hosoglu et al., 2013, Vialle-Valentin et al., 2012, Hooft et al., 2021, Brembilla et al., 2016). Additionally, children presenting with severe clinical symptoms have higher odds of antibiotic prescription (Monteiro et al., 2017, Xaba et al., 2014). A study in Uganda revealed that those who went through triage were less likely to receive inappropriate antibiotics (Means et al., 2014). In Kenya, the fear of further deterioration of the patient influenced a clinician to prescribe an antibiotic (Mekuria et al., 2019).

2.6.1.6 Laboratory findings

Investigations done on a patient including white blood cell count, ear examination, c-reactive protein test, blood culture are associated with prescribing of antibiotics (Hosoglu et al., 2013, Rebnord et al., 2017, Cartledge et al., 2020). Also, the odds of antibiotic use among those with negative malaria test is seven times the odds among those with positive malaria test (Hooft et al., 2021).

2.6.1.7 Primary diagnosis

A primary diagnosis of a bacterial illness increases the likelihood of antibiotic prescription among children (Hooft et al., 2021). Studies have shown that children diagnosed respiratory infections, urinary tract infections and acute diarrhoea have higher odds of antibiotic prescription (Covino et al., 2022, Koji et al., 2019). A diagnosis of malaria infection however reduces the odds of antibiotic use (Amponsah et al., 2021, Hooft et al., 2021, Brembilla et al., 2016).

2.6.1.8 Duration of hospital stay

Longer duration of admission was found to be associated with lower rates of antimicrobial prescription (Boone et al., 2021). In Italy however, those who stayed in hospital between eight and thirty days were 1.4 times more likely to be given antibiotics compared to those who stayed seven days or less (Ciofi Degli Atti et al., 2019).

2.6.2 Hospital-level factors

In Bangladesh, patients admitted to government health facilities have lower odds of antibiotic prescription compared to those admitted to private facilities (Boone et al., 2021). A study carried out in five Sub-Saharan African countries further showed that those seeking healthcare in public hospitals had higher odds of receiving antibiotics compared to those in public healthcare centres (Vialle-Valentin et al., 2012). The type of ward a child is admitted to also determines if they will receive antibiotic prescriptions (Ciofi Degli Atti et al., 2019). Those admitted to intensive care units, medical-subspecialty units and surgical are more likely to have antibiotic prescriptions compared to those admitted to medical units (Ciofi Degli Atti et al., 2019, Bielicki et al., 2018, Jeremiah Seni 2020). The general hospital environment and location (urban vs rural) is also considered a determinant of antibiotic prescription (Monteiro et al., 2017, Katz et al., 2020). Other factors include availability of drugs, Infection Prevention and Control (IPC), antibiotic stewardship programs, the level of training of physicians, their cadres, lack of clinical guidelines, pressure from clinic owners, high patient loads and access to diagnostics (Means et al., 2014, McKnight et al., 2019, Mekuria et al., 2019).

2.7.0 Consequences of injudicious use of antibiotics

2.7.1 Antibiotic resistance

Antibiotic resistance and the continuous spread of resistant bacteria are currently among the most significant challenges to the world's health, food security, and development (WHO, 2015). Many microorganisms in healthcare facilities are quickly becoming resistant to antibiotics (WHO, 2012). In the United States, data shows that there have been approximately two million cases of antibiotic resistant bacteria every year which has resulted in an increase of twenty billion USD in healthcare costs (CDC, 2013). Similarly, there have been about 25,000 deaths caused by multiple drug resistant infections and a healthcare cost of 1.5 billion euros in the European region (Uchil et al., 2014). Resistant infections have resulted in hospitalizations which have caused an economic burden of between 9 and 14 million dollars in Canada (Uchil et al., 2014). In India, there have been reports of high prevalence of gram-negative resistant bacteria (Ghafur et al., 2013). In addition, the prevalence of methicillin resistant *Staphylococcus aureus* being estimated at 41% (INSAR, 2013).

Countries in Africa and South-East Asia have been reported to lack established antimicrobial resistance surveillance systems due to lack of laboratory capacity to characterize antimicrobial resistant organisms from microbiological samples (WHO, 2014). A systematic review showed that up to 23 countries in Africa lack data on antimicrobial resistance (Tadesse et al., 2017). Withtin the countries with available data, *Streptococcus pneumoniae* has been reported to have a median resistance of 26.7% to penicillin (Tadesse et al., 2017). Additionally, *Escherichia coli* has been reported to be resistant to amoxicillin, trimethoprim and gentamicin at relatively high median resistance (Tadesse et al., 2017). There are also reports of resistance to carbapenems in *Acinetobacter spp*. and *Pseudomonas aeruginosa* (Tadesse et al., 2017).

In Sub-Saharan Africa, studies have shown a high level of resistance to the antibiotics that are commonly prescribed in hospitals (Leopold et al., 2014). An example is chloramphenicol resistance which was found in 90% of gram-negative infections (Leopold et al., 2014). Resistance to third generation cephalosporins is however limited in this region (Tadesse et al., 2017). A systematic review done in East Africa however reported high levels of up to 69% resistance to ceftriaxone among gram-negative infections (Ampaire et al., 2016). Proportionately high degrees of resistance to ampicillin, cotrimoxazole and gentamicin have also been reported in East Africa (Ampaire et al., 2016).

2.7.2 Adverse Drug Events

Some of the adverse drug events reported to be associated with injudicious antibiotic use are toxic effects on end-organs, allergic reactions and *clistridium difficile* infections (Tamma et al., 2017, Hensgens et al., 2012, Alshammari et al., 2014). A study in the United States indicated that parenteral vancomycin, trimethoprim-sulfamethoxazole and aminoglycosides use caused the highest rates of kidney damage in a cohort of inpatients (Tamma et al., 2017). In Malaysia however, penicillin was found to cause the highest percentage of sever adverse events (Arulappen et al., 2018). A majority of the adverse drug events associated with antibiotic use have been confirmed to result in prolonged hospitalization (Tamma et al., 2017)

2.8.0 The Clinical Information Network (CIN)

CIN is a collaboration between KEMRI-Wellcome Trust Research Program (KWTRP), Ministry of Health (MoH) Kenya, the Kenya Pediatric Association (KPA), and participating county hospitals (Tuti et al., 2016b). The CIN was instituted to improve care provided for newborns and children admitted to county hospitals. This is done through collecting and auditing routine inpatient data, after which feedback is given to hospitals (Maina et al., 2018, Irimu et al., 2018). It covers hospitals across fourteen counties in Kenya including Vihiga, Kakamega, Nairobi, Machakos, Nyeri, Kisumu, Embu, Kirinyaga, Trans Nzoia, Busia, Kiambu, Nakuru, Kakamega and Bungoma.

2.8.1 Selection of hospitals

During the process of setting up the CIN, the MoH Kenya identified twelve counties in the country to represent low and high malaria prevalent areas (Ayieko et al., 2016). Public hospitals with at least 1000 paediatric admissions per year, offering first-referral care were selected to participate in the network. By February 2014, thirteen county hospitals were part of the CIN. The network has grown over the years and was spanning twenty-two hospitals by the end of 2020 (English et al., 2021).

2.8.2 Data Collection

In CIN hospitals, data is collected at the point of patient discharge. Standard Paediatric Admission Records (PAR) (Appendix 1), approved by MoH have been adopted in the hospitals to improve documentation (Irimu et al., 2018). The data captured in the forms include patient's biodata, history, examination, diagnosis, treatment, and outcome information, which have been expressly designed to focus on the core clinical features that are important in the care of common illnesses (Tuti et al., 2016b). To reduce errors during entry, the data are captured as dichotomous fields with checkboxes and yes or no options. Data entry clerks abstract data from the PARs into a Research Electronic Data Capture (REDCap) tool (Tuti et al., 2016a, Maina et al., 2018).

As data are entered into the REDCap tool, data quality is checked using validation rules that are preprogrammed. The data are deidentified and transmitted to a central server at KTWRP daily. Here, a code generated by R software runs quality checks daily, cleans and recodes the data for easier reporting. Authentication is done by data managers who visit the hospitals periodically and re-enter randomly selected files (Tuti et al., 2016b, Maina et al., 2018).

CHAPTER THREE: METHODOLOGY

3.0 Introduction

This chapter elaborates the materials and procedures used in conducting this study. It explains in detail the study design, setting, participants, variables, statistical methods and ethical issues considered when conducting the study.

3.1 Study area

This study was conducted in twelve hospitals which are part of CIN as described in section 2.8 of literature review. They are located across 11 counties in Kenya. The hospitals include Busia County Referral Hospital, Embu Level 5 Teaching and Referral Hospital, Kakamega County General Teaching and Referral Hospital, Kerugoya County Referral Hospital, Kiambu Level 5 Hospital, Kisumu County Hospital, Kitale County Referral Hospital, Machakos Level 5 Hospital, Mama Lucy Kibaki Hospital, Mbagathi County Hospital, Nyeri County Referral Hospital and Vihiga County Referral Hospital. These are public county hospitals, formerly level 4 and 5, offering first-referral care. Each of them has more than 1,000 paediatric admissions per year with the major diagnoses being pneumonia, malaria, meningitis, malnutrition, diarrhoea and dehydration.

3.2 Study design

This was a cross-sectional analytic study. The rationale for choosing this design was that it allows for the estimation of prevalence and identification of the determinants of antibiotic prescription.

3.3 Study population

3.3.1 Target Population

The target population of this study comprised all paediatric patients (aged two months or older) admitted in paediatric wards in public hospitals in Kenya.

3.3.2 Source Population

This population included all paediatric patients aged ≥2 months, admitted in twelve CIN hospitals between 2014 and 2020.

3.4 Eligibility criteria of the study participants

3.4.1 Inclusion criteria

Patients admitted in paediatric wards in CIN hospitals from 2014 to 2020, aged ≥2 months, with treatment administered at admission were included in the study.

3.4.2 Exclusion criteria

Paediatric patients with missing information on treatment were excluded from the study.

3.5 Case definition

The cases in this study were paediatric patients with at least one antibiotic prescription at admission who met the eligibility criteria.

3.6 Sample size determination

The minimum required sample size was determined as specified by Bujang *et al* (2018) for observational studies involving multivariable logistic regression;

$$n = 100 + EPV\ (i)$$

Where

$n = the\ number\ of\ paediatric\ patients$

$EPV = the\ event\ per\ variable$

$i = the\ number\ of\ independent\ variables\ to\ be\ included\ in\ the\ model$

The recommended EPV is 50 (Bujang et al., 2018). The number of predictor variables included in the analysis based on the conceptual framework is 6. This gave a sample size of 400.

3.7 Study variables and their method of measurement

The dependent variable in this study was antibiotic prescription. The independent variables were sex, age, duration of hospital stay, type of hospital visit, diagnoses and season.

Table 2: Study variables and their method of measurement

Variable	**Method of measurement**
Outcome variable Antibiotic prescription (binary)	Patients with at least one antibiotic prescription were categorized as yes while those with no antibiotic prescription were categorized as no
Demographic characteristics Sex(binary)	This was captured as male or female
Age (continuous)	This was the age at admission of the child recorded in months

Clinical characteristics Duration of hospital stay (continuous)	 This was calculated by subtracting the date of admission from the date of discharge of the child in days.
Visit (binary)	This captured whether the child was referred from another hospital as reported by the child's caregiver during consultation. It was recorded as primary or referral.
Diagnosis (nominal)	This represented the diagnoses at admission as reported by the clinician. It was categorized as malaria only, pneumonia only, meningitis only, diarrhoea only, dehydration only,malnutrition only, malaria+comorbidities pneumonia+comorbidities, meningitis+comorbidities, diarrhoea+comorbidities, dehydration+comorbidities, malnutrition+comorbidities and other diagnoses
Season (nominal)	This represented the season of admission categorized as wet (April, May, June, October, November, December) and

	dry(January, February, March, July, August, September).

3.8 Conceptual framework

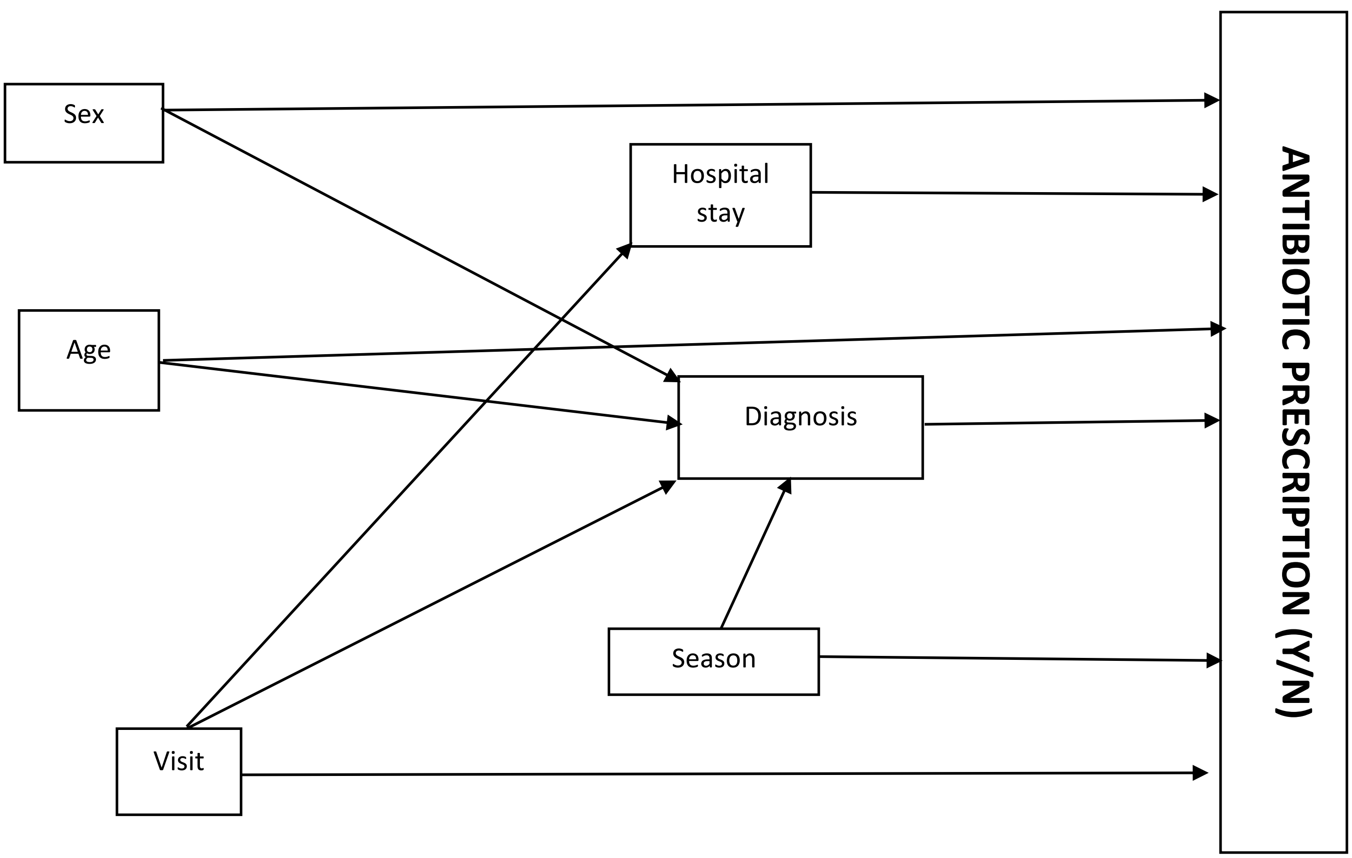

Figure 1: Causal diagram of the determinants of antibiotic prescription among children

3.9 Data abstraction plan

Data were exported from CIN's REDCap interface and saved in an Excel spreadsheet. During exportation, only variables to be used in the analysis as specified in Table 2 were selected. From Excel, the data were loaded onto R software for management and analysis.

3.10 Data processing and analysis plan

Data management involved coding of categorical variables, dealing with implausible values, identifying and classifying antibiotic prescriptions in the CIN dataset. The degree of missingness for each predictor variable was estimated.

3.1.1 Descriptive Analysis

Continuous variables were summarised using means, variances, medians and ranges. Categorical variables were summarised using percentages.

3.1.2 Inferential Analysis

The period prevalence of antibiotic prescription and its 95% exact binomial confidence interval were estimated.

For univariable analyses, a mixed-effects logistic regression model was used to determine the effect of each predictor variable on antibiotic prescription. The variable hospital was added as a random effect to account for clustering of the outcome within hospitals. Predictor variables with $p<0.2$ were included in the multivariable analysis. To control for confounding, elimination of non-significant predictor variables was only considered when their exclusion from the model did not result in >30% change in the effects of the remaining variables (Dohoo et al., 2012). Collinearity between the variables in the model was tested using a Variance Inflation Factor (VIF) threshold of

>2.5. Two-way interactions were fitted between variables in the final model and their significance assessed.

3.1.3 Minimization of errors and biases

The CIN data entry clerks were routinely trained on abstraction of data from medical records and a standard operating procedure for data entry provided as specified by Tuti *et al* (2016). Error and quality checks were done daily prior to uploading the data to the central server. The accuracy of the data was confirmed by data managers who visited the hospitals periodically and re-entered randomly selected files.

3.1.4 Ethical considerations

Ethical approval to conduct this study was granted by the Scientific and Ethical Review Unit of Kenya Medical Research Institute (KEMRI SERU, protocol no 3459) and Kenyatta National Hospital-University of Nairobi Ethics and Research Committee (KNH-UoN ERC, proposal no P414/05/2022). Data in the CIN were de-identified to ensure confidentiality.

3.1.5 Study limitations

This study did not explore the role of clinician-level factors like their cadres, level of training and guideline use which have been shown to influence antibiotic prescription in hospitals since the data are not available in the CIN database. This poses a possibility of residual confounding which might have led to overestimation of the odds ratios. Because of the potential for subjectivity in making a diagnosis, non-differential misclassification could have been introduced thus biasing the odds ratios towards the null. It was also difficult to ascertain whether certain antibiotics were prescribed due to their availability or appropriateness. Finally, the hospitals included in this study were public hospitals located in high and low malaria-endemic areas. This limits generalizability of the findings to private facilities in the country.

CHAPTER FOUR: RESULTS

4.0 Introduction

This chapter lays out the findings of this study commensurate with its objectives. The demographic and clinical characteristics of the study participants are described in detail. The commonly used classes of antibiotics, prevalence of antibiotic use and the results of the univariable and multivariable analysis are also provided.

4.1 Study population

A total of 155, 552 paediatric patients were admitted to the 12 CIN hospitals between 2014 and 2020. Of these, 14.4% (n = 22,415) who were either younger than two months or older than 18 years were excluded. An additional 16.5% (n = 25,637) with missing treatment information were also excluded, leaving 69.12% (n = 107, 500) who participated in the study (Figure 2).

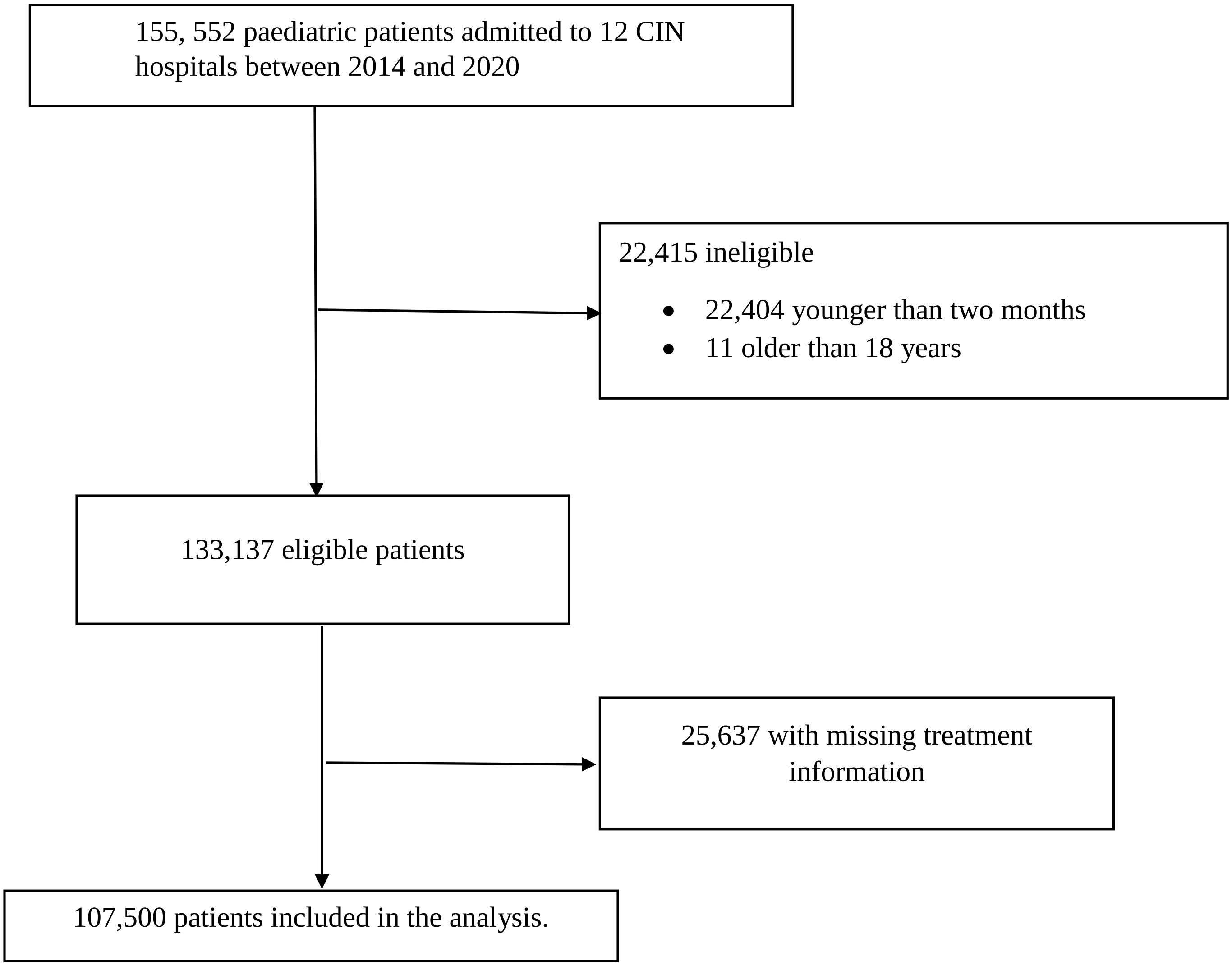

Figure 2: Patient inclusion criteria

4.2 Characteristics of the study population

The demographic and clinical characteristics of the study participants are shown in table 3. The study participants had a median age of 1.8 years (Inter-quartile range: 0.9 - 4 years). The median duration of hospital stay was 3 days (Interquartile range: 2-6 days). A majority of the children sought care in the hospitals as their primary visit (78.6%, n = 65, 698) with slightly more than half of them being admitted during the wet season (51.3%, n = 55,118). The major diagnoses were malaria and other comorbidities (20.7%, n = 22,282), pneumonia only (17.0%, n = 18,314), pneumonia and other comorbidities (15.7%, n = 16,907) and malaria only (12.1%, n = 13,024).

Table 3: Demographic and clinical characteristics of children admitted to the 12 CIN hospitals between 2014 and 2020

Variable	**Values**	**Median (Inter-quartile range)**	**Frequency n (%)**
Sex	Male Female	-	59,239(55.4) 47,724(44.6)
Age (years)		1.8(0.9 - 4)	-
Duration of hospital stay (days)		3(2-6)	-
Visit	Primary Referral	-	65, 698(78.6) 17,899(21.4)
Season	Dry Wet	- -	52,382(48.7) 55,118(51.3)
Diagnosis	Malaria only Pneumonia only Meningitis only Diarrhoea only Dehydration only Malnutrition only Malaria+comorbidities Pneumonia+comorbidities Meningitis+comorbidities Diarrhoea+comorbidities Dehydration+comorbidities Malnutrition+comorbidities Other diagnoses	- - - - - - - - - - - - -	13,024(12.1) 18,314(17.0) 4,989(4.6) 3,221(3.0) 1,142(1.1) 1,571(1.5) 22,282(20.7) 16,907(15.7) 269(0.3) 5,978(5.6) 342(0.3) 3,435(3.2) 3,967(3.7)

*Other diagnoses include anaemia, sickle cell disease, asthma, rickets, HIV and COVID-19.

4.3 Prevalence of antibiotic use

The estimated period prevalence of antibiotic prescription between 2014 and 2020 was 81.1% (95% CI: 80.9% - 81.3%).

4.4 Classes of antibiotics prescribed

4.4.1 Anatomic Therapeutic Chemical (ATC) classification

Overall, penicillins were the most prescribed totaling 42.6% (n = 70,995) of the prescriptions with most of them being benzylpenicillin (78.2%, n = 55,545). Aminoglycosides were the second most common antibiotics prescribed accounting for 26.6% (n = 44,292) prescriptions. Of the aminoglycosides, gentamicin were 89.2% (n = 39,591). Ensuing were cephalosporins (19.6%, n = 32,753) which were largely ceftriaxone (95.2%, n = 31,172. The other classes of antibiotics prescribed were imidazole derivatives (3.9%, n = 6,570) which were predominantly metronidazole, macrolides (1.5%, n = 2,500), quinolones (0.7%, n = 1211), carbapenems (0.3%, n = 460) and other systemic antibacterials (4.8%, n = 7,977) which were a group of tetracyclines, amphenicols, glycopeptides, nitrofuran derivatives and trimethoprim derivatives (Figure 3).

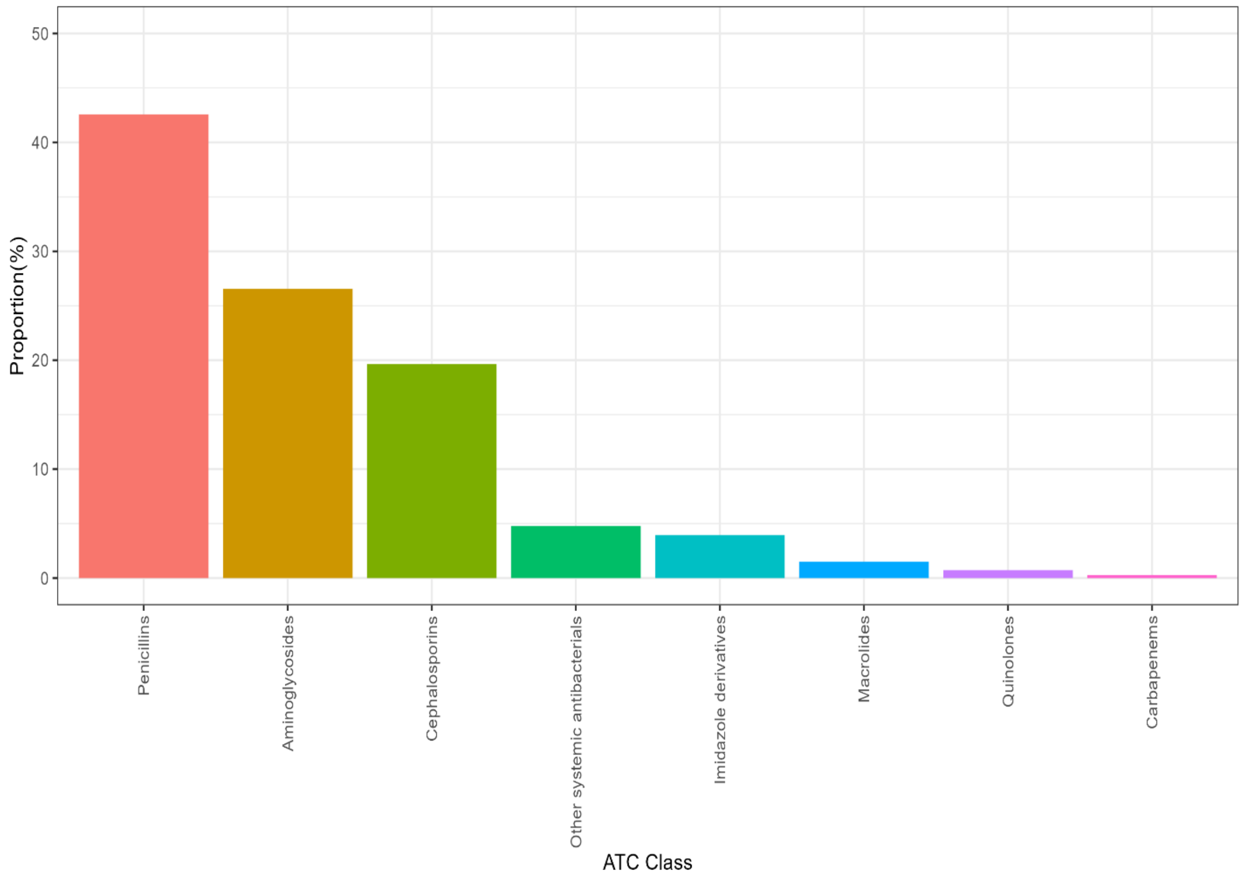

Figure 3: Proportion of antibiotics prescribed per ATC classes

4.4.2 Access, Watch and Reserve (AWaRe) classification

The most prescribed of the AWaRe antibiotics were the Access 129,473 (77.7%) followed by Watch 35,585 (21.4%) and Reserve 1,591 (0.9%) (Figure 4).

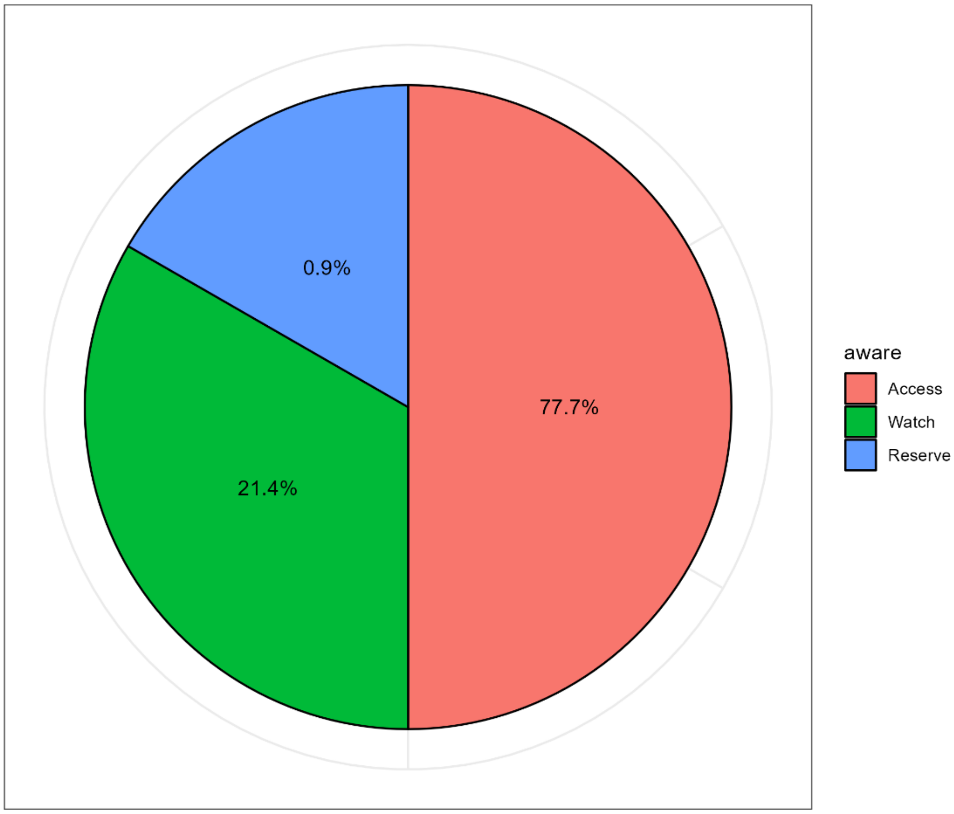

Figure 4: Proportion of antibiotics prescribed per AWaRe classes

4.5 Determinants of antibiotic prescription

According to the results of the univariable analysis of the determinants of antibiotic prescription, the variables age, duration of hospital stay, type of hospital visit, season and diagnoses were significantly associated with antibiotic prescription among children admitted to CIN hospitals at 20% level of significance (Table 4). These were subsequently added to the multivariable model.

Table 4: Univariable analysis of the determinants of antibiotic prescription among children admitted to the 12 CIN hospitals between 2014 and 2020 using mixed-effects logistic regression

Variable	**Value**	**Odds Ratio**	**95% CI**	**LRT p-value**
Sex	Female	1.0	Ref	-
	Male	1.0	0.9 -1.2	0.821
Age	<5 years	1.00	Ref	-
	≥ 5 years	0.7	0.4 - 0.9	<0.001
Duration of hospital stay	Short (0-5 days)	1.0	Ref	<0.001
	Medium (6-10 days)	5.3	4.9 - 5.6	
	Long (>10 days)	8.1	7.2 - 9.2	
Visit	Primary	1.0	Ref	-
	Referral	1.2	1.1 - 1.4	<0.001
Season	Dry	1.0	Ref	-
	Wet	1.1	1.0 - 1.3	0.017
Diagnoses	Malaria only	1.0	Ref	<0.001
	Pneumonia only	169.5	137.8 - 208.5	
	Meningitis only	39.4	32.0 - 48.5	
	Diarrhoea only	1.3	1.2 - 1.4	
	Dehydration only	1.4	1.2 - 1.6	
	Malnutrition only	23.6	18.1 - 30.9	
	Malaria+comorbidities	3.3	3.2 - 3.5	
	Pneumonia+comorbidities	115.8	95.7 - 140.2	
	Meningitis+comorbidities	46.7	21.8 - 99.7	
	Diarrhoea+comorbidities	1.5	1.4 - 1.6	
	Dehydration+comorbidities	6.3	4.4 - 8.8	
	Malnutrition+comorbidities	10.5	9.2 - 12.1	
	Other diagnoses	6.2	5.6 - 6.8	

In the multivariable analysis, only age, duration of hospital stay and diagnoses were statistically associated with antibiotic prescription at 5% level of significance (table 5). The VIF for all the variables in the model was less than 2.5 indicating low correlation between the variables.

The odds of antibiotic prescription among children aged 5 years or older was 0.8 times that of children younger than 5 years controlling for duration of hospital stay and diagnoses (OR: 0.8, 95% CI: 0.6 – 0.9). Compared to those who had a short (0 – 5 days) duration of hospital stay, those who had a medium (6 – 10 days) and long (>10 days) duration of hospital stay had 4.7(OR: 4.7, 95% CI: 4.4 – 5.1) and 7.5(OR: 7.5, 95% CI: 6.4 – 8.7) times the odds of antibiotic prescription controlling for age and diagnoses. Diagnoses were also found to associated with antibiotic prescription, controlling for age and duration of hospital stay. For instance, children diagnosed with pneumonia only had 162 times the odds of antibiotic prescription compared to those diagnosed with malaria only (OR: 162, 95% CI: 131.0 – 200.4). The odds of antibiotic prescription among those diagnosed with meningitis, malnutrition, dehydration and diarrhea were 29.2 (OR: 29.2, 95% CI: 23.7 – 36.0), 12.1 (OR: 12.1, 95% CI: 9.2 – 15.1), 1.3 (OR: 1.3, 95% CI: 1.1 – 1.5) and 1.3 (OR: 1.3, 95% CI: 1.1 – 1.4) times respectively that of those diagnosed with malaria only. Comparably, those with other diagnoses were 5.4 times more likely to receive antibiotics compared to those diagnosed with malaria only (OR: 0.8, 95% CI: 4.9 – 6.0).

Table 5: Multivariable analysis of the determinants of antibiotic prescription among children admitted to the 12 CIN hospitals between 2014 and 2020 using mixed-effects logistic regression

Variable	**Value**	**Odds Ratio**	**95% CI**	**LRT p-value**
Age	< 5 years	1.00	Ref	**-**
	≥ 5 years	0.8	0.6 - 0.9	<0.001
Duration of hospital stay	Short (0-5 days)	1.0	Ref	<0.001
	Medium (6-10 days)	4.7	4.4 - 5.1	
	Long (>10 days)	7.5	6.4 - 8.7	
Diagnoses	Malaria only	1.000	Ref	<0.001
	Pneumonia only	162.0	131.0 - 200.4	
	Meningitis only	29.2	23.7 - 36.0	
	Diarrhoea only	1.3	1.1 - 1.4	
	Dehydration only	1.3	1.1 - 1.5	
	Malnutrition only	12.1	9.2 - 15.9	
	Malaria+comorbidities	3.0	2.8 - 3.1	
	Pneumonia+comorbidities	91.5	75.6 - 110.8	
	Meningitis+comorbidities	24.8	11.0 - 55.9	
	Diarrhoea+comorbidities	1.4	1.2 - 1.5	
	Dehydration+comorbidities	4.8	3.4 - 6.8	
	Malnutrition+comorbidities	6.1	5.3 - 7.1	
	Other diagnoses	5.4	4.9 - 6.0	

CHAPTER FIVE: DISCUSSION

5.0 Introduction

This study aimed to describe the antibiotic prescription patterns and identify the determinants of antibiotic prescription among children admitted to hospitals in the clinical information network in Kenya. In this chapter, the study findings are interpreted based on the objectives of the study. Comparisons are also done with findings from other studies with similar objectives.

5.1 Prevalence of antibiotic prescription

The prevalence of antibiotic prescription among children admitted to the CIN hospitals during the study period was estimated to be 81.1%. This is consistent with other studies done in Sub-Saharan Africa which reported the prevalence of antibiotic use among children ranging from 70.6% to 98% (Labi et al., 2018, Fadare et al., 2015, Monteiro et al., 2017, Gizework and Seyfe, 2015). The prevalence of antibiotic use among children in North America and the United Kingdom are however lower, 35% and 32% respectively (Tribble et al., 2020, Gibbons et al., 2019). This difference could be attributed to the high burden infectious diseases among children in Sub-Saharan Africa which require antibiotic treatment (Williams et al., 2018). Nevertheless, there have been reports of poor regulation of antibiotic use in low income settings (Umar et al., 2018).

5.3 Classes of antibiotics prescribed

5.3.1 Anatomic Therapeutic Chemical (ATC) classification

The most prescribed ATC class of antibiotics among children admitted to the CIN hospitals was penicillins (42.6%, n = 70,995). This is consistent with studies in the United States, Germany and Italy which showed that penicillins are widely used in paediatric wards for children diagnosed with pneumonia (Kronman et al., 2011, Araujo da Silva et al., 2020, Buccellato et al., 2015). The use of penicillins is similarly common in other LMICs including Nepal, Bangladesh, Ghana and

Nigeria (Boone et al., 2021, Amponsah et al., 2021, Nepal et al., 2020, Umar et al., 2018). Benzylpenicillin was found to be the chiefly used among all the penicillins prescribed. It is the recommended primary treatment for most acute paediatric infections in combination with gentamicin in Kenya (Health, 2016). Other studies have however shown that amoxicillin is the most prescribed of all the penicillins (Hsia et al., 2019, Nepal et al., 2020).

Aminoglycosides were the second most common antibiotics prescribed accounting for 26.6% of the antibiotic prescriptions. Among them, gentamicin prescriptions were 89.2% (n = 39,591). Similar findings have been shown in HICs where aminoglycosides are among the top three prescribed classes of antibiotics for children (Osowicki et al., 2014, De Luca et al., 2016). Other studies in Sub-Saharan Africa have also shown that aminoglycosides are commonly prescribed for community acquired infections among paediatric inpatients (Labi et al., 2018). In Brazil however, they are chiefly prescribed in neonatal intensive care units.

Cephalosporins were also found to be common (19.6%, n = 32,753) and were predominantly third generation cephalosporins. Third generation cephalosporins are often prescribed for community acquired infections (Ciofi Degli Atti et al., 2019). They are the most used antibiotics in China, Saudi Arabia and Nepal (Guo et al., 2021, Kazzaz et al., 2020, Nepal et al., 2020). Their consumption has increased over the last decade owing to their favourable frequency of administration and lower costs (Maina et al., 2020). Ceftriaxone was found to be the most prescribed among the third generation cephalosporins. These finding are consistent with that of a study done in 56 countries within Africa, the Eastern Mediterranean, Europe, and Southeast Asia (Yingfen Hsia and networks, 2019). Reports show that the use of ceftriaxone is associated with increased incidence of extended-spectrum beta- lactamases which raises concerns for antibiotic resistance (Skrlin et al., 2011).

5.3.2 Access, Watch and Reserve (AWaRe) classification

According to the AWaRe classification, Access antibiotics were prescribed the most (77.7%) followed by Watch (21.4%) and Reserve (0.9%). The low use of reserve antibiotics in the CIN hospitals could be an indicator of rational antibiotic use, but it is also difficult to define the appropriate type of antibiotic to be used. A global study on antibiotic use in children showed that all countries prescribed the reserve antibiotics least, with Mexico having the highest proportion (Yingfen Hsia and networks, 2019). In Tanzania, the most prescribed antibiotics belong to the access group whereas hospitals in Uganda prescribe watch antibiotics the most with ceftriaxone accounting for the highest percentage(86.7%) (Jeremiah Seni 2020, Kiggundu et al., 2022). Ceftriaxone was reported to be used empirically as a first-line treatment for most community-acquired infections (Kiggundu et al., 2022).

5.4 Determinants of antibiotic prescription

5.4.1 Age

This study revealed that age was a significant predictor of antibiotic prescription. Children who were 5 years or older had roughly four-fifths the odds of antibiotic prescription as those younger than 5 years (OR = 0.8, 95% CI: 0.6 – 09). This could be a mirror of the higher burden of infectious diseases among children under-five which calls for the use of antibiotics (Sharrow et al., 2022). Studies in Sub-Saharan Africa have reported that children younger than 5 years receive more antibiotic prescriptions compared to other age groups (Monteiro et al., 2017, Umar et al., 2018, Labi et al., 2018, Obura et al., 2021). Age group was found to be significantly associated with antibiotic prescription in Uganda, Mozambique and Nepal (Obura et al., 2021, Monteiro et al., 2017, Nepal et al., 2020). Another study in Italy however reported that patients in older age groups, 6 – 11 years, were more likely to be prescribed antibiotics (Ciofi Degli Atti et al., 2019). This could be because Italy is a high income country with a lower burden of disease among under-five children compared to Sub-Saharan countries (Sharrow et al., 2022).

5.4.2 Duration of hospital stay

In this study, children who had medium (6 – 10 days) and long (>10 days) durations of hospital stay had higher odds of antibiotic prescription compared to those who had short (0 – 5 days) durations of hospital stay. Longer hospital stay could be due to severe illness which often requires antibiotic treatment (Birhanu et al., 2022). Some children could however stay longer in hospital to complete their treatment regimen especially if it is administered parenterally. A study in Italy revealed that those who stayed in hospital between eight and thirty days were 1.4 times more likely to be given antibiotics compared to those who stayed seven days or less (Ciofi Degli Atti et al., 2019).

5.4.3 Diagnoses

There was a significant association between diagnosis and antibiotic prescription (Table 5). Compared to children diagnosed with malaria only, those with a diagnosis of pneumonia only were 162 times more likely to be given antibiotics. The basic paediatric protocol used by clinicians in Kenyan hospitals recommends the use of the combination of penicillin and gentamicin for severe pneumonia, and oral amoxicillin for non-severe pneumonia (Health, 2016). This explains the high odds of antibiotic prescription among this group of children. Those diagnosed with pneumonia and other comorbidities, compared to those diagnosed with malaria only had 91.5 times the odds antibiotic prescription. The OR in this group is lower than that of those diagnosed with pneumonia only. It could be that the comorbidities like dehydration are not indications for antibiotic use. Studies have shown that children diagnosed with lower respiratory infections have higher odds of antibiotic prescription (Covino et al., 2022, Koji et al., 2019).

The odds of antibiotic prescription among those diagnosed with meningitis only compared to those diagnosed with malaria only was 29.2. That of those diagnosed with meningitis and other comorbidities was slightly lower. The first-line treatment for meningitis in Kenya is ceftriaxone (Health, 2016). Similarly, studies have reported that bacterial meningitis is often managed using antibiotics (Tacon and Flower, 2012, Shrestha et al., 2015).

The findings of this study showed that children with a diagnosis of either diarrhoea or dehydration had 1.3 times the odds of antibiotic prescription compared to those diagnosed with malaria. This could be an indication of irrational antibiotic use as dehydration as well as malaria are not indications for antibiotic use (Health, 2016). A study in Kenya found that injudicious use of antibiotics was common among children with diarrhoea (Rhee et al., 2019). In Ethiopia, children with acute diarrhea were reported to have higher odds of antibiotic use (Koji et al., 2019).

A diagnosis of malnutrition only compared to malaria only increased the median odds of antibiotic prescription by approximately 12-fold. The odds for those diagnosed with malnutrition and other comorbidities was lower. The basic paediatric protocol warrants the use of antibiotics in all children with severe acute malnutrition which is in line with the findings of this study (Health, 2016). It has been shown that the treatment of malnutrition with antibiotics improves the recovery and mortality rate in children (Trehan et al., 2013).

5.4.4 Type of hospital visit

From our results, the type of hospital visit, whether primary or referral was found not to influence the prescription of antibiotics among children. The reason for this could be that the patients referred from other health facilities required care that did not necessarily involve antibiotic prescription.

This finding was corroborated by a European study which reported that antibiotic prescription was similar across all referral methods (van de Maat et al., 2019).

5.4.5 Season

Season was not a significant predictor of antibiotic prescription in this study. This could be because the prevalent illnesses in the study population which are managed by antibiotics are preponderant across all seasons. A similar study in Kenya however found that the odds of prescription of antibiotics increased significantly between October and December (Hooft et al., 2021).

CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

6.0 Introduction

This chapter outlines the major findings of this study in line with the specific objectives. The recommendations are also listed in this chapter as a step towards improving antibiotic stewardship in Kenyan hospitals.

6.1 Conclusion

This study reported a high prevalence of antibiotic use of 81.1% among children admitted to the CIN hospitals in Kenya between 2014 and 2020.

The most commonly prescribed ATC classes of antibiotics were penicillins, aminoglycosides and cephalosporins. According to AWaRe classification, Access antibiotics were prescribed the most followed by Watch and Reserve antibiotics respectively.

The factors associated with antibiotic prescription among children admitted to CIN hospitals were age, duration of hospital stay and diagnosis.

6.2 Recommendations

In view of the findings of this study, the following recommendations were made in order to improve antibiotic use in CIN hospitals:

1. Given that diagnoses like dehydration increased the odds of antibiotic use yet they are not indications for antibiotic use, appropriate treatment guidelines should be availed in the hospitals and the clinicians trained on judicious antibiotic use.

2. The high prevalence of antibiotic use could have been aided by inadequate laboratory capacity. There is need to improve diagnostic support in order to inform rational prescription of antibiotics.

3. Strategies should be put in place to ensure adherence to treatment guidelines by the clinicians.

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8.0 APPENDICES

Appendix 1: Paediatric Admission Record

Name		**IP No.**		**Ward**			
Contact (Tel)		Relation		DOB	dd/mm/yyyy		
Admission Date	dd /mm / yyyy	Sex	M ☐ F ☐	Age		months	
County		Subcounty/ Constituency		Location		Sub- location	
Village		Nearest Health Facility		Nearest School			
Is this first admission since birth?	Y☐ N☐	No of previous admissions		Date of last admission	dd/mm/yyyy		
Re-admission to this hospital?	Y☐ N ☐	Discharged <1 month ago	Y☐N ☐				
Is child referred from another health facility?	Y ☐ N☐	Date first treated in other facility	dd/mm/yyyy				
Presenting Complaints							

History

Weight	Kg	**Height / Length**	cm	*WHZ score*		MUAC (cm)		**Head Circum** (cm)	

Length of illness	days	
Fever – No. of days =	**Y**☐	**N**☐
Cough– No. of days =	**Y**☐	**N**☐
Cough > 2 weeks	**Y**☐	**N**☐
Contact with TB /Chronic cough	**Y**☐	**N**☐
Difficulty breathing	**Y**☐	**N**☐
Diarrhoea No. of days =	**Y**☐	**N**☐
Diarrhoea > 14d	**Y**☐	**N**☐
Diarrhoea bloody	**Y**☐	**N**☐
Vomiting, No / 24hrs =	**Y**☐	**N**☐
Vomits everything	**Y**☐	**N**☐

Immunization

Vaccination card available? **Y**☐ **N**☐

as child received any vaccinations since birth? **Y** ☐ ☐

Vaccine	Received	Date received
BCG	**Y**☐ **N**☐ Don't Know ☐	dd /mm / yyyy
OPV 0(Birth)	**Y**☐ **N**☐ Don't Know ☐	dd /mm / yyyy
OPV/Penta/PCV 1	**Y**☐ **N**☐ Don't Know ☐	dd /mm / yyyy
Rota 1	**Y**☐ **N**☐ Don't Know ☐	dd /mm / yyyy
OPV/Penta/PCV 2	**Y**☐ **N**☐ Don't Know ☐	dd /mm / yyyy
Rota 2	**Y**☐ **N**☐ Don't Know ☐	dd /mm / yyyy
OPV/Penta/PCV 3	**Y**☐ **N**☐ Don't Know ☐	dd /mm / yyyy
IPV	**Y**☐ **N**☐ Don't Know ☐	dd /mm / yyyy
RTS,S 1(Malaria)	**Y**☐ **N**☐ Don't Know ☐	dd /mm / yyyy

Difficulty feeding	Y☐	N☐
Convulsions Number in last 24hrs =	Y☐	N☐
Partial / focal fits?	Y☐	N☐
Passing blood/tea/cola coloured	Y☐	N☐
Sleeps under mosquito	Y☐	N☐
Managed in isolation?	Y☐	N☐
Date of isolation:	dd /mm / yyyy	
Pre- existing illness	None ☐	
Drugs taken last 2 weeks	None ☐	
Any vaccine reaction suspected?	Y ☐ N☐ If yes, indicate most recent vaccine:	

Additional history of presenting illness;

Vitamin A given within last 6months? **Y**☐ **N**☐

Birth/ Antenatal History

aternal PMTCT status: ☐ Positive ☐ Negative ☐ Unknown

Growth and Development:

Family/Social history:

Nutritional history:

Review of Systems:
Respiratory including

ENT Cardiovascular

Gastro-intestinal / Genitourinary

Examination

Vital Signs	**Temp**	**⁰C**	**Resp Rate**	bpm	**HR**	/min	**O2 Sat**	%	**BP**

General Examination

Oral thrush **Y**☐ **N**☐ Lymph N > 1cm **Y**☐ **N**☐

Finger Clubbing Y☐ N☐

Abdomen

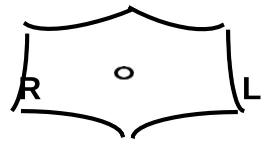
Rt **Lt**

Eye signs of malnutrition?

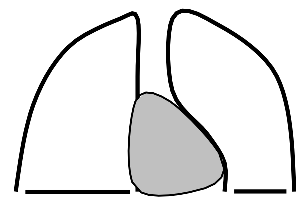
Pus☐ ulceration☐ None☐

Jaundice		**Y☐**	**N☐**
Oedema (tick all that apply)	☐None ☐Foot ☐Knee ☐Face		
A	Stridor	**Y☐**	**N☐**
B	Central Cyanosis	**Y☐**	**N☐**
	Indrawing	**Y☐**	**N☐**
	Grunting	**Y☐**	**N☐**
	Acidotic breathing	**Y☐**	**N☐**
	Wheeze	**Y☐**	**N☐**
	Crackles	**Y☐**	**N☐**
Circ & Dehy dr'n	Peripheral Pulse	☐Normal	☐ Weak
	Cap Refill	secs	*X = not possible*
	Skin warm at:	☐ Hand ☐ Elbow ☐Shoulder	
	Pallor / Anaemia	0☐ +☐ +++☐	
	Sunken eyes	**Y☐**	**N☐**
	Skin pinch (sec)	**0** **1**	**≥ 2**
D	**AVPU**	**A** **V** **P**	**U**
	Can drink / breastfeed?	**Y☐**	**N☐**
	Stiff neck	**Y☐**	**N☐**
	Bulging fontanelle	**Y☐**	**N☐**
	Can sit without support during this illness	**Y☐**	**N☐**
Infant < 1yr	Irritable	**Y☐**	**N☐**
	Reduced movement / tone	**Y☐**	**N☐**
	Umbilicus	Normal ☐ Pus ☐	Pus & red skin ☐

Chest



Front



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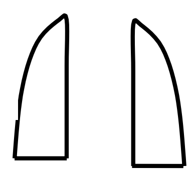

CVS

Blantyre Coma Score=______

Posture (tick that apply)

Blood/tea/cola coloured urine observed?

Y☐ N ☐ Urine

					not seen ☐ **Bones & Joints** Wrist / Rib signs Rickets **Y**☐ **N** ☐

ENT exam	**Neurological Examination (normal, increased↑, reduced↓)**
Rt Ear Lt Ear Nose Throat	

	Normal	**Right side**		**Left side**	
		Upper limb	Lower limb	Upper limb	Lower limb
Power:					
Tone:					
Reflexes:					
Plantar responses:					
Senstation:					

Summary of presentation & problems

....
....
....
....

Investigations Ordered (record subsequent tests and all results in medical record)

Malaria	☐ Blood slide ☐ Rapid Test	***Glucose***	☐ Stick test ☐ Laboratory
Haematology	☐ Hb ☐ Full haemogram ☐ PCV	***Chemistry***	☐ Na/K ☐ U&C ☐ Ca+Phos ☐ Alb ☐ LFT
If full heamogram	WBC count ______per litre		Lymphocyte count_____ per µl/mm³ _______%
	Neutrophil count________ per µl/mm³		Platelets ____________ per litre

	________%		
Microbiology	☐ Lumbar Puncture ☐ Blood Culture	***HIV***	☐ Rapid test ☐ PCR
X-Ray	☐ CXR ☐Wrist Other=	***Urine***	☐ Urinalysis ☐ Micro & culture
TB Test	☐ Microscopy for AAFBs ☐Mantoux ☐ Xpert MTB/RIF ☐ *Myco.TB* culture	***Stool***	☐ Microscopy ☐ Micro & culture
		Other	
COVID-19 Test	☐Yes	If no, why?	

Date(s) of specimen collection:	**Results**
Date specimen send to the lab: ____	Lab results: ☐ +ve ☐ -ve ☐ Inconclusive ☐ Unknown Date lab results were received: ____________dd /mm / yyyy

Admission Diagnoses – Select ONE *primary diagnosis (tick box indicating "1") and ANY secondary diagnoses (tick box indicating "2"), then indicate level of severity or type of disease if required*

Malaria	1 ☐ 2 ☐	☐ Severe ☐ Non-severe	***Anaemia***	1 ☐ 2 ☐	☐ Severe ☐ Non-severe
Pneumonia	1 ☐ 2 ☐	☐ Severe ☐ Non-severe	***Sickle cell disease***	1 ☐ 2 ☐	
Diarrhoea	1 ☐ 2 ☐	☐ Non-bloody ☐ Bloody (dysentery)	***Meningitis***	1 ☐ 2 ☐	
Dehydration	1 ☐ 2 ☐	☐ Shock ☐ Severe ☐ Some ☐ None	***Rickets***	1 ☐ 2 ☐	
HIV result		☐ Positive ☐ Exposed /PMTCT + ☐ Negative ☐ Declined test ☐On HAART ☐ indeterminate	***Asthma***	1☐ 2☐	☐ Severe ☐ Mild/moderate
Malnutrition	1 ☐ 2 ☐	☐ Kwash ☐ Marasm ☐ M. Kwash ☐ Moderate malnutrition ☐mild/none	***Suspected TB***	1 ☐ 2 ☐	
			Prematurity / LBW	1 ☐ 2 ☐	
Other 1	1 ☐ 2 ☐		***Neonatal sepsis***	1 ☐ 2 ☐	
Other 2	1 ☐ 2 ☐		**Suspected COVID-19**	1 ☐ 2 ☐	

Clinician sign -------------- Date ----/-----/-------- Time------------(am/pm)

Appendix 2: SERU Approval letter

KENYA MEDICAL RESEARCH INSTITUTE

P.O. Box 54840-00200, NAIROBI, Kenya
Tel: (254) 2722541, 2713349, 0722-205901,0733-400003, Fax: (254) (020) 2720030
Email: director@kemri.org, info@kemri.org, Website. www.kemri.org

KEMRI/RES/7/3/1 **May 0 7 , 2020**

TO: **PROF. MIKE ENGLISH**
PRINCIPAL INVESTIGATOR.

THROUGH: THE DIRECTOR, CGMR-C
KILIFI

Dear Sir,

RE: SERU PROTOCOL NO. 3459 (REQUEST FOR ANNUAL RENEWAL): A CLINICAL INFORMATION NETWORK- A TECHNICAL COLLABORATION WITH THE MINISTRY OF HEALTH AND COUNTY HOSPITALS TO SUPPORT AND IMPROVE STRATEGIES FOR AUDIT AND HEALTH SERVICE EVALUATION

Thank you for the continuing review report for the period **May 11, 2019** to **March 23, 2020**.

This is to inform you that the Expedited Review Team of the KEMRI Scientific and Ethics Review Unit (SERU) was of the informed opinion that the progress made during the reported period is satisfactory. The study has therefore been **granted approval**.

This approval is valid from **May 11, 2020** through to **May 10, 2021**. Please note that authorization to conduct this study will automatically expire on **May 10, 2021**. If you plan to continue with data collection or analysis beyond this date please submit an application for continuing approval to the SERU by **March 29, 2021**.

You are required to submit any proposed changes to this study to the SERU for review and the changes should not be initiated until written approval from the SERU is received. Please note that any unanticipated problems resulting from the implementation of this study should be brought to the attention of the SERU and you should advise them when the study is completed or discontinued.

You may continue with the study.

Yours faithfully,

ENOCK KEBENEI,
THE ACTING HEAD,
KEMRI SCIENTIFIC AND ETHICS REVIEW UNIT.

In Search of Better Health

Appendix 3: KNH-UoN ERC Approval Letter

UNIVERSITY OF NAIROBI
FACULTY OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
Tel:(254-020) 2726300 Ext 44355

KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/352

16th September, 2022

16 SEP 2022

Rachael Otuko
Reg. No.H57/37753/2020
Dept. of Public and Global Health
Faculty of Health Sciences
University of Nairobi

Dear Rachael,

RESEARCH PROPOSAL: PREVALENCE AND DETERMINANTS OF ANTIBIOTIC PRESCRIPTION AMONG CHILDREN ADMITTED IN TWENTY KENYAN HOSPITALS (P414/05/2022)

This is to inform you that KNH-UoN ERC has reviewed and approved your above research proposal. Your application approval number is **P414/05/2022.** The approval period is 16th September 2022 – 15th September 2023.

This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, MTA) will be used.
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by KNH-UoN ERC.
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to KNH-UoN ERC 72 hours of notification.
iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH-UoN ERC within 72 hours.
v. Clearance for export of biological specimens must be obtained from relevant institutions.
vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal.
vii. Submission of an executive summary report within 90 days upon completion of the study to KNH-UoN ERC.

Protect to discover

Turnitin Originality Report

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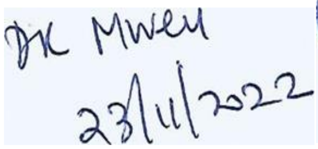
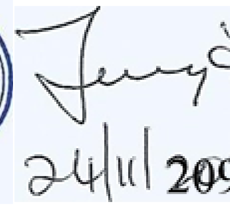
PREVALENCE AND DETERMINANTS OF ANTIBIOTIC PRE... By Rachel Otuko

Similarity Index 



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