

COMPARATIVE STUDY OF ANTIMICROBIAL USE IN HIV  
INFECTED/EXPOSED AND NON INFECTED CHILDREN AT  
NAIVASHA DISTRICT HOSPITAL, KENYA

*! dissertation submitted in partial fulfillment of the requirements for the award of the degree of  
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## DECLARATION

This dissertation is my original work and has not been presented anywhere else.

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## DEDICATION

I dedicate this book to the rocks and pillars of my life Isabelle and Isaiah; to my parents Mr and Mrs Charles Nguri, to my brothers and sisters and to the paediatric patients of Naivasha District Hospital.

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## **ABSTRACT**

Background: Antimicrobial use in HIV exposed and infected children aged below 5 years is a very frequent occurrence in clinical practice. However, frequent, unwarranted, and inappropriate use of these drugs has been on the rise bringing about issues of worldwide concern which include drug resistance. There are limited studies which show differences in antimicrobial prescribing patterns among different populations and hence the basis of a comparative study.

Objective of the study: The objective of the study was to compare antimicrobial prescribing patterns between HIV exposed/infected and HIV negative patients.

Eligibility Criteria: HIV exposed/infected and HIV negative children aged below 5 years attending Naivasha District Hospital during the study period were eligible for the study.

Methodology: The study was a hospital based cross sectional survey. It was divided into two parts: comparative survey of prescribing patterns and in-depth interview with prescribers. Data was collected on antimicrobials prescribed between 1<sup>st</sup> June and 30<sup>th</sup> July 2012. The antibiotic choice, dosing and frequency was determined from the World Health Organization guidelines and compared to the prescribed drugs and dosages to determine appropriateness of use.

Quantitative data was analyzed using SPSS version 18.0 software; comparative chi-square test was done. Qualitative data was also analyzed, themes were mapped and content analysis done.

Justification: The World Health Organization cites significant existing gaps in the evidence for management of pneumonia, diarrhoea and other acute and opportunistic infections in HIV-infected/exposed infants and children. The study sought to identify existing differences in the management of these common childhood diseases, hence, the results will aid in the formulation of clinical practice interventions in order to improve therapy and outcomes in the study setting.

Results: The study found an existing difference in the prescribing pattern of antibiotics between HIV exposed/infected and non HIV infected children. There were 12 antibiotics prescribed to the HIV non infected children; a much wider range as compared to only 3 types of antibiotics prescribed HIV exposed/infected patients. The first 3 most commonly prescribed antibiotics in both clinical settings were cotrimoxazole, amoxicillin and ampicillin/cloxacillin. Only 20.5% of the antibiotic prescriptions in FOPC complied with the WHO guidelines. Prescriptions of HIV exposed patients were 90 times more likely to comply to the guidelines OR 90.3 95% CI: (36.4-223.8). HIV infected patients had the prescriptions with the highest occurrence of errors with the wrong frequency and duration. Lower Cadres of health workers were associated with more than 80% of the prescriptions that did not comply with the guidelines.

Conclusion: Prescriptions for HIV exposed/infected children were more likely to comply with the World Health Organization Guidelines for choice of antibiotics compared to the HIV non infected children. However, HIV exposed/infected children were also more likely to receive antibiotic prescriptions with the wrong dose. This could significantly lead to ineffective prophylaxis and management of opportunistic infections. Amoxicillin was the most commonly prescribed antibiotic and also the most irrationally prescribed in both clinical settings. This was mostly associated with the lower cadres of health workers.

## LIST OF ABBREVIATIONS

ADRs	Adverse Drug Reactions
AIDS	Acquired Immune Deficiency Syndrome
CCC	Comprehensive Care clinic . •
CTX	Cotrimoxazole
ELIDLIZ	Essential drug list of Zimbabwe
ERC	Ethics Review Committee
GIT	Gastro-intestinal Tract
GOPC	General Outpatient Clinic
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
IATT	Inter Agency Task Team on Prevention of HIV Transmission
IMCI	Integrated Management of Childhood Illnesses
KEMSA	Kenya Medical Supplies Agency
KNH	Keuyatta National Hospital
LRTI	Lower Respiratory Tract Infection
MOMS	Ministry of Medical Services
MSH	Management Sciences for Health
NASCOP	National Aids and STI Control Program
OIs	Opportunistic Infections
PCP	<i>Pneumocystis Jiroveci</i> Pneumonia
PMTCT	Prevention of Mother To Child Transmission

POPC	Paediatric Out Patient Clinic
RPM	Rational Pharmaceutical Management
SMX	Sulphamethoxazole
spp	Species
TMP	Trimethoprim
UoN	University of Nairobi
URTI	Upper Respiratory Tract Infection
USA	United States of America
WHO	World Health Organization

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## CHAPTER ONE

### INTRODUCTION

The Inter Agency Task Team on Prevention of Human Immunodeficiency Virus (HIV) Transmission in pregnant women, mothers and their children (IATT) has proposed a four-pronged approach for the prevention of HIV transmission that targets non-pregnant and pregnant women, mothers and their children. These four prongs are: primary prevention of HIV infection in women, prevention of unintended pregnancy among HIV-infected women, interventions to reduce transmission from HIV-infected pregnant and lactating women to their children and care and support of women, children and families infected and affected by HIV and AIDS (The PMTCT-plus) [1]. Prompt prevention and treatment of bacterial and opportunistic infections among HIV exposed and infected children is covered in the fourth prong. Cotrimoxazole and dapsone are recommended for prophylaxis of *Pneumocystis Jirovecii* Pneumonia (PGP) and other infections like non-typhoid salmonella. Certain infections such as oral thrush have been suggested to increase the risk of transmission of HIV from mother to a breastfeeding child. Frequent antibiotic use has been associated with a risk of developing oral and laryngeal thrush [2, 3].

Antibiotics use continues to be a major issue of concern to health care policy makers due to the cost implications and the emergence of antimicrobial resistance. Kenya has not been spared from this, with majority of the population accessing the health care from public health facilities with limited availability and sometimes erratic supply of drugs. The problem of resistance to antimicrobial drugs is particularly troublesome in developing countries. The underlying problems are largely economic and societal, and no ready solutions are available. An urgent need exists for more appropriate selection and use of antimicrobial drugs in the developing countries.



The focus of developing countries should be on the availability of safe and effective drugs and on the enforcement of more responsible national drug policies.

In pediatrics in particular, major issues of concern are dose adjustments with age, disease and weight. The occurrence of polypharmacy (when more than one drug is prescribed, often unnecessarily, for one condition), is also a big problem in the current health care setting in Kenya

#### 1.1.1 Types of irrational prescribing

Common forms of irrational prescribing include the use of drugs when there is no indication. A common example is the use of antibiotics for the management of viral upper respiratory infections such as influenza. Antibiotics are frequently inappropriately used to manage childhood diarrhea which should be ideally managed using Oral Rehydration Salts (ORS).

The use of drugs with doubtful or unproven efficacy and safety constitutes inappropriate drug selection. An example is the use of antimotility agents for management of diarrhea. Often correct drugs may be selected but are wrongly administered at incorrect dosages and duration. In hospitalized patients intravenous or injectable formulations are often administered when oral formulations would be appropriate. The use of unnecessarily expensive drugs such as, third generation, broad spectrum antimicrobial drugs when a first line, narrow spectrum agent is indicated is an example of inappropriate drug selection [4],

### 1.1.2 Reasons for irrational use of drugs

The major forces that affect rational use of drugs can be categorized as those derived from patients, prescribers, the work place, the supply system including industry influences, regulation, drug information and misinformation and combinations of several other factors. Patient misinformation, misleading beliefs, patient demands/ expectation also influence drug prescribing practices. Prescribers may also lack information and may be inadequately trained on drug use.

Difficulties in establishing the cause of the pneumonia in infants with HIV infection has been cited as a contributory factor to lack of adherence to standard treatment guidelines [5], They may also lack objective drug information, have limited experience as well as be influenced by misleading beliefs about drug efficacy. Other factors like the status of existing drug supply systems with unreliable suppliers causing drug stock-outs and shortages or at extreme cases supply of expired drugs may also influence prescribing practices. Drug regulation may lead to non-essential drugs being available as well as lack of regulation enforcement on drug use. Drug industries also serve as a major prescriber influencing medium with promotional activities and misleading claims. Failure to provide available, safe and effective drugs is often an impetus for irrational drug use [4].

### 1.1.3 Irrational Prescribing of Antibiotics

The World Health Organization (WHO) estimates that more than half of all medicines are prescribed, dispensed or sold inappropriately and that half of all patients fail to take them correctly. The overuse, underuse or misuse of medicines results in wastage of scarce resources and widespread health hazards [6]. Inappropriate use of antimicrobial puts the community at risk

of severe illness or death as a result of unbeatable infections, and squanders limited healthcare resources for health care [7].

Notably, qualified Health Care Workers (HCWs) make minor errors when second-line drugs are in stock and more major errors when second-line drugs are not in stock [8]. Antibiotic use in hospitals in developing countries is not well documented [9]. Studies in India have reported irrational practices such as; polypharmacy, overuse of antibiotics and injections and prescribing using proprietary names and unnecessarily prolonged drug use [ 10, II J.

Indicators of rational drug use have worsened over the past decade despite the implementation of managerial, regulatory and training interventions, with the rates for inappropriate prescribing and dispensing practices and prevalence of self-medication with antimicrobials and herbal products being alarmingly high. Management Sciences for Health (MSH) in Lusaka Zambia reported that 13.3% of patients were proscribed antibiotics for a number of conditions for which did not merit the drugs. This included antibiotics prescribed for diarrhoea, malaria and non-pneumonia coughs [12].

A study done in Sudan concluded there was a lot of irrational drug use among children. The treatment guidelines for respiratory illness and diarrhoea were not followed [13]. MSH Rational Pharmaceutical Management (RPM) Project, in its pharmaceutical sector assessment of 1998 in Ghana, determined that there were several problems that had a negative impact on prescribing practices in the public sector. Prescribing problems were defined as high numbers of drugs per prescription, high prescribing rates for antibiotics and injections and cost [14],

A study in Atlanta, Georgia found that based on temperature, leukocyte count, and the presence or absence of a focus, ceftriaxone use, as compared with practice guidelines, was questionable in 19%, and not justified in more than 60% of the patients. For patients who received ceftriaxone more than once, its use was justified in only 13%. Results of blood cultures were positive in only 1% of the patients [15]. Qualitative research suggests that, over time, physicians tend to "soften" to patients' demands for antibiotics and that they engage less frequently in patient education to reduce their short-term workload [16].

#### 1.1.4 Non-prescription Use of Antibiotics

Increased antibiotic prescription might increase self-medication with antibiotics [17]. Non-prescription antimicrobials are associated with very short courses and inappropriate drug and dose choice. Many studies involving non prescription dispensing have shown short, often single day, courses of antimicrobials with the dose being commonly lower than standard doses [18]. Patients who were prescribed antibiotics for a sore throat stated that they were more likely to consult a health professional to request antibiotics the next time they developed a sore throat [17, 19].

Some surveys in Europe have also shown that parents have unrealistic demands for antibiotics, where more than 50% of the respondents definitely expected an antibiotic for the treatment of flu, ear ache and all ear infections [20]. Between 22 and 70% of parents have misconceptions about the appropriate applications and efficacy of antibiotics and often use them without a prescription [21, 22].

Leftover antibiotics may be available because of over-prescription or patient non-compliance with a course of treatment [19]. Clinicians also report that they often prescribe antibiotics

because they perceive that patients want them [ 17, 23], At the same time, physicians with higher practice volumes are more likely to prescribe antibiotics inappropriately [23],

Surveys in Europe show that many people seeking medical care because of cough and sputum production request to be treated with antibiotics [20] while general community surveys in Nigeria and Sudan focused on non-prescription use of antimicrobials have reported frequency of antimicrobial use from 48% over 1 month to 100% lifetime use [18]. A systematic review on non-prescription antibiotic use revealed that the occurrence of potential adverse events were common. Pharmacists dispensing non-prescription antimicrobials had no knowledge of patients' allergies most of the time. Non-prescription use of substandard antimicrobials is probably more common [18].

#### 1.1.5 Consequences of irrational antibiotic use

A study done in Nigeria, testing the resistance rates of highly prescribed and consumed antibiotics in a university teaching hospital in Lagos found that increased consumption of ciprofloxacin and ceftazidime correlated with increased resistance rates [24], Increasing the use of ceftazidime and ciprofloxacin has been associated with increased resistance rates for ceftazidime resistant *Klebsiella pneumonia* and ciprofloxacin resistant *P. aeruginosa* [25]. Furthermore, the consumption of ciprofloxacin was significantly correlated to imipenem resistance in *P. aeruginosa*. This underscores the urgent need for interventions like formulation of antibiotic policies and education and training of health care workers on the appropriate use of antibiotics to reduce the development of resistance. Inappropriate antimicrobial use by patients with true bacterial infections is associated with treatment failure and masking of the underlying clinical syndrome [26].

## **C H A P T E R T W O**

### **L I T E R A T U R E R E V I E W**

#### 2.1 Epidemiology of pediatric HIV infection in Africa and Kenya

Sub-Saharan Africa remains the region most heavily affected by HIV worldwide, accounting for over two thirds (67%) of all people living with HIV and for nearly three quarters (72%) of Acquired Immune Deficiency Syndrome(AIDS) -related deaths in 2008 [27], The Central Bureau of Statistics, Kenya, in 2002, states that HIV/AIDS will continue to slow down the rate of population increase. Projections estimated that over the period 2001 -20, HIV/AIDS mortality would reduce population by 5.1 million people. Infant and child mortality rates in Kenya are increasing and this is attributed mainly to HIV/AIDS [28], HIV infection and AIDS continue to pose challenges to child survival and development and impact on the nutritional status of children and incidence of common infections [29],

#### 2.2 Indications for antimicrobial use in HIV/AIDS

Oral candidiasis, pulmonary tuberculosis, recurrent respiratory infections, bacterial skin infections, and chronic diarrhoea among others have been found to be the most common clinical manifestations of HIV infected children [30].

In the pre-antiretroviral treatment era and before development of potent combination highly active antiretroviral treatment (HAART) regimens, opportunistic infections (OIs) were the primary cause of death in HIV infected children".

Children with HIV disease initially present with common childhood infections, which then recur with more frequency and severity. As the immune status deteriorates opportunistic infections (OIs) become more common. Common OIs in children include bacterial pneumonia, *Pneumocystis jiroveci* pneumonia, and diarrhoeal infections [28]. An important mode of acquisition of OIs, as well as HIV infection among children, is from their infected mother; Uninfected women co-infected with opportunistic pathogens might be more likely than women without HIV infection to transmit these infections to their infants [31].

Serious bacterial infections are a major source of morbidity and mortality in HIV-infected children. The spectrum of disease is wide, and responsible organisms vary according to the setting. The use of antibiotic prophylaxis and the emergence of multi-drug resistant bacteria necessitate examination of responsible organisms and their antibiotic susceptibility [3].

Undiagnosed, antiretroviral-naive, HIV-infected infants still present sporadically with OIs such as *Pneumocystis jiroveci* and cytomegalovirus pneumonia. HIV-infected children have a greater burden of disease due to viral, bacterial, and fungal sepsis, and the case fatality rate for non-opportunistic infections may be greater than in non-HIV-infected children. In resource limited settings, with limited access to Highly Active Anti-Retroviral Therapy (HAART), the natural history of HIV infection has been altered very little, with the majority of infected children dying from either opportunistic or non-opportunistic disease before 3 years of age [7].

### 2.2.1 Non Opportunistic infections in pediatric patients with HIV/AIDS

The risk of septicemia is higher in HIV-infected children. Just like fever, the aetiology can vary widely so it is critical to be highly suspicious of septicemia. Bacteremia occurs without any focus or secondary to infection of the lung, gastrointestinal tract, skin, ear, sinuses, and urinary tract.

Most common causative organism is *Streptococcus pneumoniae* [27], High prevalence of *Staphylococcus aureus* bacteremia has been documented among children with a high risk for acquiring infections [32].

Pneumonia remains a major cause of death and hospitalization, particularly in sub-Saharan Africa, where the pediatric HIV epidemic is concentrated. HIV-infected children have a higher risk of developing pneumonia and of more severe disease than immunocompetent children [33].

The incidence of bacteremic severe LRTI in children is greater in HIV-1-infected than in uninfected children. The most common causative agents include: *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, *Staphylococcus aureus* and *Escherichia coli* [34].

The most common form of acute gastrointestinal infection is gastroenteritis, causing diarrhoea with or without vomiting [35]. Enteroaggregative *Escherichia coli* (EAEC) have been implicated in acute and persistent diarrhoea in HIV/AIDS patients. On the other hand, non-typhoidal *Salmonella* species have been shown to be one of the main causes of bacterial bloodstream infections in children in sub-Saharan Africa, and HIV infection is a risk factor [36], Few studies have linked HIV infection to dysentery in children, and there is little evidence of a



different spectrum of etiological agents in bloody diarrhoea in HIV-infected or -exposed patients [37,38],

Infections of the skin and the soft tissues beneath are common. A wide range of bacteria have been recovered from skin and soft tissue infections, the majority are caused by the Gram-positive cocci *Staphylococcus aureus* and *Streptococcus pyogenes*. Although soft tissue infections are the most common manifestation of *S. aureus* disease, numerous other sites can be affected [35].

Acute meningitis is the most common bacterial disease affecting the central nervous system, which causes about 175 000 deaths per year, predominantly in the developing world. Epidemic meningitis due to *Neisseria meningitidis* (usually group A) is common in a broad belt across sub-Saharan Africa and is also seen in parts of Asia [35].

### 2.2.2 Opportunistic infections in paediatric patients with HIV/AIDS

The most common opportunistic infections among HIV positive children are: PCP, cryptococcal meningitis, pulmonary tuberculosis, oral and esophageal candidiasis among others [35].

If untreated, mortality due to *Pneumocystis jiroveci* (previously *P. carinii*) Pneumonia can be as high as 100%. Therefore it remains imperative to have a high index of suspicion for PCP and to diagnose and treat as early as possible. It is caused by the fungus *Pneumocystis jiroveci*, a ubiquitous organism that usually causes primary infection in early childhood.

### 2.3 Drug resistance to antibiotics in paediatric HIV/AIDS in Africa

The use and misuse of antimicrobials has driven the relentless expansion of resistant microbes leading to a loss of efficacy of these "miracle drugs" [39]. Respiratory tract infections are a frequent cause of medical consultations. This has resulted in widespread use of antibiotics, and is a primary factor that drives the emergence of antibiotic resistance. Recent surveys suggest that the proportion of patients with influenza-like illness who receives antibiotics is at least double the actual incidence of the infections for which the treatment is intended [10].

There is at least one study which has documented antibiotic resistance among HIV-1 infected children. This was done in South Africa and showed that 60% of *S. aureus* and 85.7% of *E. coli* isolates were resistant to methicillin and trimethoprim-sulfamethoxazole, respectively [34]. The rest of the studies were not done among HIV positive children. Gram-negative bacilli causing invasive bacterial disease have been studied in Kenya, against the antibiotics in common use. Susceptibility to amoxicillin, cefotaxime and ciprofloxacin were 28%, 95% and 99% respectively. Susceptibilities for isolates from children aged less than 14 days were: chloramphenicol, 81%; trimethoprim/sulfamethoxazole, 71%; and gentamicin, 91%. From older children, susceptibilities were: chloramphenicol, 62%; trimethoprim/sulfamethoxazole, 39%; and gentamicin, 73%. The combination of gentamicin and chloramphenicol covered 91% of all isolates. Age was the only clinical feature that predicted resistance [40].

There are other studies on antibiotic resistance, but most were not done among HIV positive or exposed children. Bwayo *et al* carried out another study in Nairobi between 1991 and 1995, with a total of 1659 positive cultures comprising 30 different bacterial species. Out of the overall

gram negative isolates (61.9%), *E.coli* and *Klebsiella* spp formed over 70%. Among the gram positive, *Staphylococcus aureus*, *Enterococcus* and coagulase negative *staphylococcus* species (spp) constituting 41%, 26% and 18% respectively were the most common. Most organisms showed multiple resistance patterns to commonly used antimicrobials similar to hospital acquired infections. The gram negative Isolates were resistant to cotrimoxazole, ampicillin, tetracyclines, chloramphenicol, and sulphamethoxazole. However, the sensitivity of these organisms to gentamycin and kanamycin was between 60 and 90%. Among the gram positive isolates, there was a high resistance to penicillin and tetracyclines (60-90%). All isolates were, however, highly sensitive to cephalosporins and fluoroquinolones. Indiscriminate use of antibiotics in the community may have selected for resistance [41].

Another study carried out in a hospital in Kamataka, South India, on antibiotic sensitivity on bacteria from stool isolates [42], revealed that the majority of the isolates were resistant to the commonly used antibiotics. A considerable number of isolates were resistant to nalidixic acid, ampicillin, and trimethoprim-sulfamethoxazole. Most isolated strains showed similar susceptibility patterns. Resistance to three antimicrobial drugs (multidrug resistance) was observed in 75% of the isolates. The most common multidrug resistance profiles encountered in this study include a combination of tetracycline, cotrimoxazole, nalidixic acid, ampicillin, cefotaxime and cefuroxime. Most of the isolates showing multidrug resistance pattern were from children below 5 years of age.

#### 2.4 Guidelines for antibiotic use in HIV/AIDS infected or exposed children

The WHO Guidelines for the Integrated Management of Childhood Illnesses (IMCI) [43] guidelines are appended in Appendix D. These give a guide on antibiotic selection in paediatric patients.

The most widely used antibiotic worldwide in the HIV-infected population is trimethoprim-sulfamethoxazole (TMP-SMX) which is used as prophylaxis for *Pneumocystis jiroveci* pneumonia (PCP). Its additional prophylactic activity against toxoplasmosis and its antibacterial activity against a number of important bacterial pathogens including *Salmonella* spp. and *Streptococcus pneumoniae* has led to a general decrease in the number of life-threatening bacterial infections occurring in patients with advanced HIV infection, particularly in resource-poor settings, although the rates have not decreased to those seen in the HIV-negative population [44].

#### 2.5 Drug Utilization Reviews of Antimicrobials in HIV/AIDS patients

Mutua in her study [45], done at Kenyatta National Hospital (KNH), described the management of opportunistic infections among HIV positive children. Over 100 prescription errors were identified, out of a total of one thousand and thirty drug prescriptions reviewed. Antibiotics were among the most prescribed drugs (25.4%). Amoxicillin, erythromycin and cotrimoxazole, prescribed for prophylaxis, were found to be the most commonly prescribed antibiotics. Cotrimoxazole had the highest number of incorrect doses for a single drug. Erythromycin and amoxicillin were found to be most common inappropriately prescribed antibiotics.

Similarly, a retrospective study done in a paediatric emergency department in Barcelona, Spain, found that out of 73% patients for whom antibiotics were prescribed, therapy was considered to be inappropriate. Treatment was unnecessary in some cases and in others the antibiotic selected was incorrect. The treatment length was wrong in a section of the patients, and inappropriately short in all of them [46],

A survey carried out in France indicated that a high percentage of antibiotic prescriptions were below the recommended doses, particularly in children [20]. A case series study in paediatric medical wards of two University Teaching Hospitals in Harare Zimbabwe [5], studied antibiotic use in infants hospitalized with HIV-related pneumonia. Fifty four percent of cases received penicillin, aminoglycoside and cotrimoxazole and overall only 30% of prescriptions complied with Essential Drug List of Zimbabwe (F.D.I.Z) recommendations for treatment of severe pneumonia in children with HIV infection. The difficulties in establishing the cause of the pneumonia in infants with HIV infection was a contributory factor to lack of adherence to standard treatment guidelines.

An audit on antibiotic use in patients hospitalized for 5 days or more was conducted in two teaching hospitals in Indonesia [47]. A high proportion of patients were found to have received antibiotics, out of which more than thirty percent had an unclear indication. Aminopenicillins accounted for more than fifty percent of the antibiotics prescribed, and cephalosporins (mostly third generation), accounted for more than a quarter of the total proportion. Predictors of antibiotic use were diagnosis of infection, stay in surgical or paediatric departments, low-cost nursing care, and urban residence. Only 21% of prescriptions were considered to be definitely

appropriate; the rest were inappropriate regarding choice, dosage or duration, and more than forty percent of prescriptions, were deemed to be unnecessary. This study focused on patients hospitalized for long duration, a situation which may include patients with chronic diseases and HIV may fall in such a category.

More than seventy percent of the patients surveyed in a teaching hospital in Gondar, Ethiopia, had more than one antibiotic prescribed [48]. The antibacterials most frequently prescribed were penicillin G, chloramphenicol, and ampicillin. More than eighty percent of the antibiotic exposures were found to be in the pediatric ward.

## **2.6 PROBLEM STATEMENT**

Effective implementation of the fourth prong of the PMTCT guidelines (PMTCT-plus) is being compromised by lack of clear guidelines on antibiotic use, lack of baseline studies on the current management strategies, prescribing patterns, dosing accuracy and patient compliance. This may promote transmission and compromise prophylaxis of PCP and other infections among HIV infected and exposed children. It is probable that clinicians under the PMTCT programme over prescribe antibiotics in comparison to their colleagues managing infectious diseases in non-HIV patients. Hence the need for a study that describes and compares antibiotic use in the two clinical settings.

The use of drugs by injection is common in developing countries. Healthcare providers unnecessarily prescribe injections to patients suggesting that patients ask for injections [49],

The recommended treatment outlined for various common infectious diseases in childhood is described in the PMTCT guidelines. Unfortunately correct dosing in paediatrics is often a

problem due to limited clinician knowledge on drug-dose selection. In the instance of cotrimoxazole the recommended dosing of cotrimoxazole may not be easily accessible to clinicians and may be inaccurately prescribed in the absence of data on the child's weight.

The PMTCT guidelines fall short of providing guidance for various doses of various antibiotics for use in management of infections in paediatric patients in HIV. In the management of conditions such as oral thrush, the choice of drug is left at the discretion of clinicians. The WHO Integrated Management of Childhood Illnesses (IMCI) guidelines give a more detailed approach.

In the absence of local guidelines for management of infectious diseases in HIV positive patients, it is necessary to carry out a drug utilization review of antibiotic use in HIV infected and exposed children. Under the PMTCT-plus programme, antibiotics are available free of charge and this may promote irrational use and thus may lead to oral thrush, in turn leading to risk of transmission of HIV. It is therefore necessary to compare the antibiotic prescribing patterns in children under the PMTCT plus programme and those managed within a typical treatment setting.

Although there is no Kenyan data, one may find that many people may take antibiotics before admission.

## 2.7 JUSTIFICATION OF THE STUDY

HIV-infected infants frequently present to health services for the first time with a life-threatening critical illness. This problem is magnified several fold in high-prevalence developing regions, where rationing of resources for those who might derive maximal benefit is an inescapable necessity [50].

Prevention and management of Opportunistic Infections (OIs) remain critical components of care for HIV-infected children. OIs continue to be the presenting symptom of HIV infection among children whose HIV-exposure status is not known [27]. The roll out of pediatric HIV care and treatment is faced with many challenges. Lack of skills of health professionals, prescriber attitude and practices to manage cases is one of the main drawbacks, and plays a big role in the increase in under 5 mortality in Kenya. Currently, data that shows differences in the quality of prescribing between HIV infected and non infected children is scarce. There is therefore a need for a study that seeks to describe the existence of differences in the quality of care and the reasons for such differences. In line with that, WHO cites significant existing gaps in the evidence for management of pneumonia, diarrhoea and other infections in HIV-infected and exposed infants and children. Hence, the results will aid in the formulation of clinical practice interventions in order to improve therapy and outcomes in the study setting. This study revealed gaps in infectious disease management in HIV- infected and exposed children. Identification of these differences is likely to lead to modification of guidelines so as to improve treatment outcomes in HIV-infected and exposed children.



## **2.8 AIMS AND OBJECTIVES:**

The overall aim of this study was to compare antibiotic use and prescribing practices for HIV infected/exposed children and non-HIV infected children at the Naivasha District Hospital, (in the former) Rift Valley Province, Kenya. In addition, risk factors and health care provider-related causes for irrational antibiotic prescribing were identified.

### Specific Objectives

The specific objectives of the study were to:

1. To determine the antibiotic prescribing trends/profiles among HIV infected/exposed and non HIV infected children.
2. To establish any inappropriate prescribing practices with respect to the management of children infected and exposed to HIV.
3. Describe the risk factors for irrational antibiotic use at die Comprehensive Care Clinic (CCC) at Naivasha district hospital.
4. Identify prescriber related factors for irrational use of antibiotics.

## **CHAPTER THREE**

### **MATERIALS AND METHODS**

The study was carried out in 2 parts. The first part was a prescription survey aimed at identifying prescribing patterns, prevalence of irrational prescribing and comparing drug use in HIV exposed/infected and Non-HIV infected children. The second was an in-depth interview with prescribers from the two clinical settings which explored the prescriber related factors for irrational use of antibiotics.

#### **3.1 Comparative survey of prescribing patterns**

##### **3.1.1 Study Site**

The study was carried out at the Naivasha District Hospital CCC and the general outpatient paediatric clinic. The general paediatric ward generally has more of patients with stage 4 disease and were therefore excluded. Naivasha District Hospital is the second largest hospital in Nakuru county, in the former Rift Valley province. It is a public Hospital run by the Ministry of Medical Services, located in Sokoni Location, I-akeview Sub location.

The hospital has pre-natal bed capacity of 16 and post-delivery bed capacity of 16. The newborn unit has a cot capacity of 15 with 200 percent occupancy in the year 2010. The facility's Comprehensive Care Centre (CCC) serves as both a primary care centre and public referral centre for mothers and children affected and infected by HIV/AIDS. The clinic offers separate services for children and adults. Currently, the centre has approximately four thousand HIV infected adults and over four hundred HIV positive children enrolled for care. I'MTCT services

are carried out in Maternity, Child Welfare Clinic (CWC), the Comprehensive Care Clinic and the Pharmacy. Both HIV exposed and infected children are seen at the CCC.

Review was done only in outpatient setting because PMTCT services are mainly provided in this area as opposed to the ward which focuses on curative services in children at stage 3 and 4 disease.

### 3.1.2 Study population

The study population was all the prescriptions from children aged below 5 years seen at the CCC and at the General outpatient Paediatric clinic during the period between 1<sup>st</sup> June and 30<sup>th</sup> July **2012**.

### 3.1.3 Study design

This was a hospital-based comparative cross sectional survey. Prescriptions received at the paediatric pharmacies at the 2 sites were reviewed as they are filled. Prescriptions from patients on the PMTCT-plus programme were obtained from the pharmacy designated for patients on HAART and PMTCT services. Prescriptions for patients attending the POPC were obtained from the main pharmacy designated for paediatric patients.

### 3.1.4 Sampling procedure

#### 3.1.4.1 Sampling plan

Samples were taken on 2 days each week, to include a busy day and a non-busy day. Data was collected from the CCC pharmacy on Wednesdays when the paediatric CCC clinic took place.

From Health Information Management System 2010, Naivasha, the facility had 466 children under care in CCC under the PMTCT plus program, by June 2010.

#### 3.1.4.2 Sample size determination

It was hypothesized that the prevalence of irrational antibiotic use in HIV infected/exposed children was 15% higher than the prevalence of irrational antibiotic use in HIV negative children. As per Kenya Service Provision Assessment which studied the rate of irrational (unwarranted) antibiotic use in public health facilities in Kenya the prevalence of irrational antibiotic use in general population was found to be 67% [51]. The study was designed to detect a 15% difference in the prevalence of irrational antibiotic use with a 95% confidence level.

Since the study was a comparative survey, the following estimation by precision formula was used [52]:

$$N = \frac{(Z_1 + Z_2)^2 \cdot 2 \cdot (SD)^2}{(P_1 - P_2)^2}$$

Where:

N= sample size

SD~ estimated standard deviation based on a previous study

Z<sub>1</sub>= Z value from statistical tables corresponding to level of significance (α) (1.96)

Z<sub>2</sub> Z value from statistical tables corresponding to the probability of type II errors (0.84)

P<sub>1</sub>=, Expected proportion of irrationally prescribed antibiotics in the CCC arm (0.82)

p<sub>2</sub>= Expected proportion of irrationally prescribed antibiotics in the GOPC arm (0.67)

Assumptions:

The level of power = 80% (0.84)

Level of significance (alpha) = 0.05 (1.96)

Rate of irrational antibiotic use in HIV negative = 67% as per Kenya Service Provision Assessment which studied the rate of irrational (unwarranted) antibiotic use in public health facilities in Kenya.

Rate of antibiotic use in HIV positive = 82% (or 15% higher)

Therefore:

$$N = \frac{Z_{\alpha/2}^2 \cdot 2 \cdot (SD)^2}{(P1 - P2)^2}$$
$$(1.964 \cdot 0.84)^2 \cdot (2 \cdot 0.745 \cdot 0.255)$$
$$(0.82 - 0.67)^2$$

N=145 prescriptions per arm

Therefore a minimum of 145 prescriptions was sampled from each study arm.

### 3.1.4.3 Sampling of prescriptions

Sampling was done over a period of 2 months so as to minimize the effects of seasonal change on disease. Sampling was done for prescriptions issued in June and July. From discussions with clinicians at the study site, every week, about 100 prescriptions are processed at the CCC which was running on Wednesdays. The OP clinic received 100 prescriptions every 2 days.

#### 3.1.4.4 Selection of prescriptions

Prescriptions were selected first based on the age of the patient. Prescriptions for patients whose age falls in the 0-5 year category were selected. Those that have antibiotics were then selected. The OP numbers of the randomly selected prescriptions were given to the records of Yicc for retrieval of patient files.

#### 3.1.5 Selection Criteria

##### Inclusion criteria

1. Prescriptions from patients seen in the CCC and POPC between the 1<sup>st</sup> June and 30<sup>th</sup> July 2012
2. Prescriptions from patients aged between 0 to 5 years
3. Prescriptions from patients who had been prescribed any antimicrobial drug

##### Exclusion criteria

1. Prescriptions from patients admitted in to the wards
2. Prescriptions from patients with incomplete files

#### 3.1.6 Data collection and Materials

A pre-designed data collection form was used to collect the relevant data on patient demographics, antibiotic dosing and diagnosis. (Appendix D) Prescriptions were obtained from the outpatient pharmacy. Patient's HIV status and diagnosis was obtained from the sampled patient files. For each antibiotic prescribed to each patient, the doses prescribed, the formulation and the frequency of administration was documented. In addition, for each prescription, the presence of an injectable drug was documented. The prescribed antibiotics were compared the recommendations in the WHO guidelines.

### Prc-testing of data collection form

The data collection form was piloted by randomly selecting 10 prescriptions of patients registered in CCC and 10 patients attending the POPC. The data was entered into the form to test its suitability in data collection. The form was then modified to ensure that it conformed to the Naivasha district hospital records format and was able to accurately pick the data as recorded in the prescriptions and files.

#### 3.1.7 Definition of cases

The following criterion was used to define cases:

HIV exposed/positive patients included all patients seen at the CCC. In addition the health records indicated that the child was either HIV positive or their mother was recorded as being HIV positive.

HIV negative cases included any child seen at the POPC. Any child seen at the POPC whose health records indicated that he/she was HIV positive was excluded. In addition, patients seen at the POPC whose records indicated that the mother was HIV positive were excluded from the study.

A HIV exposed child was defined as a child seen in the CCC whose record in the file show that the mother is HIV positive. In addition a child whose HIV status is recorded as "exposed" in the CCC file will be considered as HIV exposed.

Dosages were considered as correct if they were prescribed at the WHO recommended frequency of administration and dosage for the age and weight of the child.

Wrong doses prescribed and wrong frequencies were considered as inappropriate prescribing.

An injectable antibiotic was considered as inappropriately prescribed if they were not in line with the WHO guidelines.

Irrational prescribing was defined as any antibiotic prescription that did not conform to the WHO guidelines. An antibiotic was considered as irrationally prescribed if: there was lack of an indication, was not the drug of choice as per the guidelines, dose was not correctly adjusted, and the frequency and duration was not as per guidelines and was prescribed in an incorrect formulation.

Incomplete files and prescriptions were defined as those with missing data and information.

#### 3.1.5 Variables

The dependent variables included any prescription that was irrational or containing a wrong dose and/or wrong frequency.

The independent variables included: risks for irrational prescribing: day seen (busy day), cadre of prescriber, HIV status of child, education status of prescriber, age of the child, diagnosis and record of previous use of non-prescription antibiotics.

#### 3.1.6 Quantitative data Analysis

All variables were subjected to descriptive data analysis. For continuous variables, the median and interquartile ranges (IQR) was reported. Categorical variables were reported as proportions of various components and the 95% confidence interval (95% CI). Pearson Chi square test was done to compare the distribution of various variables across clinical settings, Kruskal-Wallis test was used to test for difference across the two different settings for continuous variables. The risk factors for incorrect dosing were determined using logistic regression. Step-wise model building



was used to identify the most important risk factors for incorrect dosing. Data was analyzed using SPSS version 18.0 software. P-values of less than 0.05 were considered statistically significant.

### 3.2 In Depth Interview with Prescribers

The second part of the study involved in depth interviews with prescribers. An in depth interview was carried from one prescriber from each one of the following cadres: clinical pharmacists, nurses, clinical officers and physicians. Six prescribers were interviewed. The objective was to identify factors that may have influenced the choice of antibiotic and irrational prescribing.

#### 3.2.1 Study design

This was a qualitative cross sectional survey.

#### 3.2.2 Study site

The study site was the same as for the comparative cross sectional survey of prescriptions described above.

#### 3.2.2 Study population

Prescribers (physicians, nurses and clinical officers) and Clinical Pharmacists who were offering services at the Naivasha District Hospital and the CCC during the months of study.

#### 3.2.3 Sample size determination

Principles of sample size determination were used to determine the sample size. Six health care providers was sampled which was the recommended number for in depth interviews [55]. However, sampling stopped when a concept or theme was saturated.

### 3.2.4 Sampling Procedure

From a baseline survey conducted in Naivasha in 2010 by Partnership for Medical Education Kenya (Prime-K), the facility has 1 pediatrician, 4 pharmacists, 5 medical officers, 150 nurses (40 bachelors' degree holders, 35 diploma holders, and 75 certificate holders), and 13 Clinical officers. Purposeful sampling was done [53] so that at least one member of each cadre was represented. 1 nursing officer, 1 nursing officer intern, 1 clinical pharmacist, 1 medical officer, 1 medical officer intern and 1 clinical officer were sampled. Therefore 6 prescribers were interviewed. Sampling took place from both clinical settings- the CCC and the POPC.

### 3.2.5 Selection Criteria

#### Inclusion Criteria

1. Health workers who were working in the hospital at either of the 2 clinics between June and July 2012
2. Health workers who consented to be interviewed.

#### Exclusion criteria

1. Health workers who declined/ do not give consent to be interviewed.
2. Health workers not working in the CCC or the POPC at the time of the study.
3. Administrators who did not provide direct clinical services.

### 3.3 Data collection

Informed consent was obtained before the start of each interview. The Health Care Provider was allowed to select an interview date, time and venue that are convenient for him/her. The interview was recorded using a digital voice recorder and manually by pen and paper. The recording was explained clearly through the consent process, after which the participant signed

prior to the beginning of the interview. The interview was unstructured and guided by the appended interview guide (Appendix D). The guide was designed to collect information on factors that determined choice of antibiotic, factors that may influence prescribing patterns in the two different clinical setting and level of adherence to the national treatment guidelines. The digital recording was then transcribed on to a Microsoft word program.

### 3.4 Qualitative data analysis

Data collected was transcribed on to a computer, onto Microsoft word software, then classified into themes and mapped using charts to define concepts. The themes were coded after reading of the transcripts and analyzed to define results. Content analysis was done according to the guidelines by William Miller and Benjamin Crabtree [54],

\* i . \* \*

### 3.5 Data Management and Quality Assurance for the Prescription Survey and In depth Interviews

#### 3.5.1 Data management

All data from the prescription survey and the in depth interviews were entered into a MS-Access database and a MS Word document on to a computer respectively. Data cleaning and validation was performed to achieve a clean dataset that was then be exported into SPSS version 18.0 program. Back up files were stored in a CD and flash disk. This was done regularly to avoid loss or tampering.

### 3.5.2 Quality Assurance

The data collection forms and the interview guide were evaluated using a pilot study. The findings of the study were used to modify the data collection instruments. The research assistants were trained with the guidance of a trainee Standard Operating Procedure. The level of training was considered sufficient if the degree of inter data collector agreement was 85%. Two data collectors were present during the in depth interview. One of the researchers was recording the proceedings of the interview, while the other was manually conducting the interview. The hand written notes were compared to the transcribed version and serious inconsistencies in the content were noted and discussed with the supervisor. Interviews were transcribed on the same day of the interview so as to capture all non-verbal and verbal interactions during the interview and to avoid loss of information. Each digital recording was transcribed by at least two transcribers who were Kenyans and were therefore conversant the local English dialect. With the level of agreement between the two transcribers, the 2 transcribed copies were compared and any major inconsistencies were noted. A code book was then used to guide coding and identification of themes. The research progress was monitored once a week by the study supervisor.

## 3.6 Ethical considerations

Permission to carry out the study was obtained from the UoN/KNH Ethics and Research committee at Kenyatta National Hospital.

### 3.6.1 Confidentiality

The review of patient files was done within the respective departments at the Naivasha District Hospital. All data obtained was kept under lock and key in password protected computer files to

restrict access. Data forms did not bear patients' name or clinic numbers and the patients were only be identified by study numbers. Participants of the in depth interview did not have their names mentioned nor their pictures taken.

### 3.6.2 Benefits from the study

There were no direct benefits to the participants. However, the findings will be communicated to the primary care givers to contribute in improving the quality of PMTCT services offered at Naivasha District Hospital.

### 3.6.3 Risks to the participants

Since the in depth interview and the prescription survey did not include any intervention, this was a minimal risk study.

### 3.6.4 Voluntariness and Informed Consent

Consent was obtained in writing after adequate explanation for enrollment in this study. At any stage the participant was free to withdraw from the study without penalty.

### 3.7 Study Limitations

It was difficult to confirm HIV status of children seen at POPC as there were no confirmatory HIV tests that were done. This limitation was minimized by excluding any patient with a record of confirmed HIV positive status from the POPC. This being a retrospective study, the health records were also inaccurate or incomplete. All incomplete records were excluded from the study. Participants may have been uneasy with the fact that they were aware that they were being recorded. This could have possibly altered information while conducting the recorded interviews. This was minimized by the use of a small mini recorder that was not so conspicuous during the

interview. Non-prescription use of antibiotics was also to be a limitation to the study. This was minimized by checking patient records for any reported previous use of non-prescription antibiotics.

## CHAPTER FOUR

### RESULTS AND DISCUSSION

#### <sup>m</sup> PART ONE: QUANTITATIVE SURVEY OF PRESCRIBING PRACTICES

##### 4.1 Basic characteristics of paediatric HIV positive and negative patients at Naivasha District Hospital

Between June and July 2012, 315 prescriptions from both Paediatric Out Patient Clinic (POPC) and Comprehensive Care Clinic (CCC) were evaluated for inclusion in the survey and 298 met the selection criteria. Among these, 147 were from CCC and 151 from POPC. The prescription selection process is shown in Figure 1.

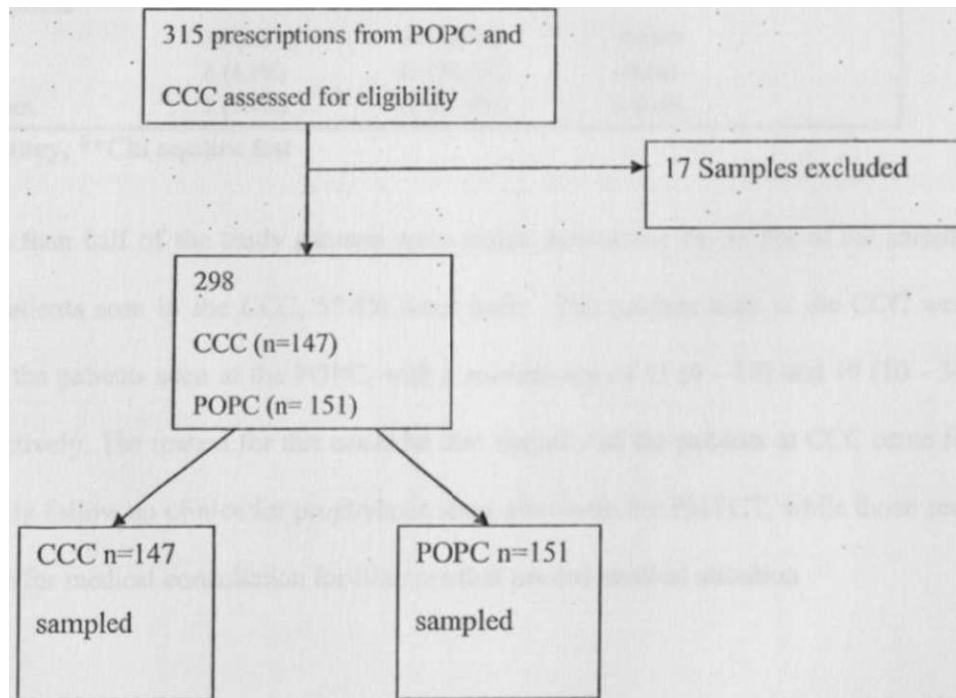


Figure 1: Consort diagram for the prescription selection process

The baseline characteristics of the patients included in the study are described in Table I below.

Table I: Basic characteristics of paediatric HIV positive patients at Nalvasha District Hospital

	Clinical setting		P value
	CCC (n= 147)	POPC (n- 151)	
<b>Age in months, Median (IQR)</b>	<b>11 (6 -18)</b>	<b>19(10-34)</b>	<b>0.0001*</b>
<b>Sex</b>			
<b>Male</b>	<b>85 (57.8%)</b>	<b>74 (49%)</b>	<b>0.127"</b>
<b>Diagnosis</b>			
<b>URTI</b>	<b>8(12.1%)</b>	<b>80 (53.3%)</b>	<b>&lt;0.001"</b>
<b>GIT</b>	<b>1 (1.5%)</b>	<b>19(12.7%)</b>	
<b>Other</b>	<b>57 (86.4%)</b>	<b>51 (34.0%)</b>	
<b>HIV AIDS status</b>			
<b>Negative</b>	<b>0</b>	<b>151 (100%)</b>	<b>NA</b>
<b>Positive</b>	<b>51 (34.7%)</b>	<b>0</b>	
<b>Unknown</b>	<b>96(65.3%)</b>	<b>0</b>	
<b>Presenting complains</b>			
<b>Cough</b>	<b>10(6.8%)</b>	<b>105 (69.1)</b>	<b>&lt;0.001</b>
<b>Fever</b>	<b>6(4.1%)</b>	<b>43 (28.3%)</b>	<b>&lt;0.001</b>
<b>Diarrhoea</b>	<b>2(1.4%)</b>	<b>27(17.8%)</b>	<b>&lt;0.001</b>

\* Mann-Whitney, \*\*Chi square test

Slightly more than half of the study patients were males accounting for 53.3% of the sample. Among the patients seen in the CCC, 57.8% were male. The patients seen at the CCC were younger than the patients seen at the POPC, with a median age of 11 (6 - 18) and 19 (10 - 34) months respectively. The reason for this could be that majority of the patients at CCC came for routine monthly follow up clinics for prophylaxis soon after birth for PMTCT, while those seen at POPC came for medical consultation for illnesses that needed medical attention.

Upper Respiratory Tract Infections and GIT conditions had a low prevalence amongst the HIV positive children. This is consistent with studies done among HIV positive children that demonstrated a lower rate of bacterial infections among children on cotrimoxazole prophylaxis,



and a lower rate of antibiotic use in this group [56, 57]. There were 8 (12.1%) patients with URTI among the CCC patient setting compared to 80 (53.3%) patients in POPC. On the other hand, there was 1 (1.5%) patient in the CCC and 19 (12.7%) patients in the POPC setting with a diagnosis of GIT conditions. Only 18 out of 147 children seen at CCC had a presenting complaint in their records. Most were coming for a routine visit to collect ARVs and therefore did not present with a complaint. The most common presenting complaint was cough with 105 (69.1%) patients in POPC and 10 (6.8%) patients in the CCC setting, followed by fever and diarrhoea respectively in both arms. In the CCC setting 6 (4.1%) patients and 43 (28.3%) patients presented with fever; 2 (1.4%) patients in the CCC and 27 (17.8%) patients in the POPC had diarrhoea. Other presenting complaints and diagnosis accounted for 21.3% of the reason for consultation which were: routine prophylaxis (20.4%) and pneumonia (8.3%).

The HIV status of the majority (65.3%) of children in the CCC setting was unknown. This is possibly because the majority of the patients surveyed were younger than 18 months before which the HIV status of a child cannot be fully determined through antibody testing and Polymerase Chain Reaction (PCR) testing which is unavailable at the study setting.

#### 4.1.1: Prescriber Characteristics

The characteristics of prescribers responsible for antimicrobial prescriptions for HIV infected/exposed children and non infected children at Naivasha District Hospital is shown in Table 2.

**Table 2:** Characteristics of prescribers responsible for antimicrobial prescriptions for HIV infected/ exposed children and non infected children at Naivasha District Hospital

	Clinical setting		P value
	CCC	POPC	
<b>Sex (n = 138)</b>			
<b>Male</b>	24 (60%)	44 (44.9%)	0.107*
<b>Female</b>	16(40%)	54(55.1%)	
<b>Prescription by Cadre (n = 211)</b>			
<b>Medical officer</b>	41 (68.3%)	17(11.3%)	<0.001*
<b>Clinical officer</b>	12(20%)	134 (88.7%)	
<b>Nurse</b>	7(11.6%)	0 (0%)	

\* Chi square test

In the CCC setting, medical officers generated 68.3% of the prescriptions compared to only 11.3% of the prescriptions in POPC. Important to note, is that nurses issued prescriptions in the CCC while in POPC setting no nurse issued a prescription. The reason for this could be because majority of the HIV exposed infants are seen during immunization visits which is convenient for the mother. Most of these immunization clinics are run by nurses. It is also worthwhile to note that majority of the CCCs in public hospitals are run by nurses and especially the PMTCT clinics. From the data presented one cannot draw conclusions about the adequacy of staffing since the case load in the two settings was not studied.

#### 4.2 Types of Antibiotics Prescribed

Most (88%) patients received one antibiotic, 9.4% received two antibiotics and 2.3% of them received 3 antibiotics. The two most commonly prescribed antibiotics were cotrimoxazole and amoxicillin prescribed in 59.5% and 22.5% of the total prescriptions in the two populations.

In the CCC setting, cotrimoxazole was prescribed to 99.3% of the patients while in the POPC setting, it was prescribed in 22.8% of the prescriptions surveyed.

The range of antibiotics prescribed in the CCC was narrow compared to the range prescribed in the POPC. Only 3 different antibiotics were commonly prescribed frequently in the CCC as compared to the 12 prescribed in the POPC. The commonly prescribed antibiotics in the CCC were cotrimoxazole 59.4%, amoxicillin (22.5%) and ampicillin/cloxacillin (4.0%) respectively. This is not surprising as cotrimoxazole is the first line drug of choice for prophylaxis against PCP, toxoplasmosis, malaria and a range of other bacterial infections in CCCs [56, 57, 60], This finding is also similar to a study in New York in four HIV clinics which also found cotrimoxazole to be the most frequently prescribed prophylactic antibiotic among HIV positive patients [60]. The other antibiotics were prescribed at frequencies less than 4 %. These included: Flucloxacillin, flucloxacillin/amoxicillin, benzylpenicillin, amoxicillin/clavulanic acid, ceftriaxone, ampicillin, chloramphenicol and erythromycin. These drugs are listed in the Kenya Essential Drug List (KEDL) and in the KEMSA drug supply list and were therefore expected to be available at the pharmacy in the study setting.

The most frequently prescribed drug in POPC was amoxicillin at 41.7% followed by cotrimoxazole at 22.8%. Consistent with this, the Specialist Advisory Committee on Antimicrobial Resistance (SACAR) Paediatric Subgroup has also found amoxicillin accounting for the bulk of all the antibacterial prescriptions in other countries [62], A country to country comparison of antibiotic prescribing shows a striking similar trend; liquid amoxicillin prescriptions represented more than half of all antibiotics prescribed. As was the case with this study, amoxicillin was prescribed mainly for minor upper respiratory tract infections. It is worth

noting from literature, that amoxicillin has been particularly identified and recommended for a significant reduction strategy in prescribing, and it is being overprescribed. This could increase the chance of development of bacterial resistance to amoxicillin in children.

A wider range of antibiotics was prescribed in the POPC setting as compared to the CCC setting. The range of antibiotics prescribed in the POPC was; cotrimoxazole 22.8%, amoxicillin 41.7%, ampicillin/cloxacillin 7.3%, flucloxacillin 5.3%. Flucloxacillin/amoxicillin, benzylpenicillin, amoxicillin/clavulanic acid, ceftriaxone, ampicillin, chloramphenicol and erythromycin were prescribed at a rate of between 4-0.7% each. In the CCC only 3 drugs were prescribed; cotrimoxazole 95.9%, amoxicillin 3.4% and ampicillin/cloxacillin 0.7%. This is probably because CCC is a specialized clinic where most of the children are either HIV positive or exposed and supplied with a narrow range of antibiotics that probably limits them to prescribe only the available ones. The POPC patients came presenting with a wider range of complaints unlike in the CCC setting.

Amongst the patients who received more than one antibiotic, benzyl penicillin was the most frequently prescribed agent at POPC. It was probably given to children with more severe illnesses as a bolus initial dose.

Thirteen children received amoxicillin in addition to cotrimoxazole, while 6 patients in POPC received 3 antibiotics as opposed to only one child in the CCC setting.

Table 3: Types of antibiotics prescribed

First antibiotic	POPC	CCC	Total
Cotrimoxazole	36 (2.8%)	141 (95.9%)	177(59.4%)
Amoxicillin	62 (41.7%)	5 (3.4%)	67 (22.5%)
Ampicillin/cloxacillin	11 (7.3%)	1 (0.7%)	12(4.0%)
Flucloxacillin	8(5.3%)		8 (2.7%)
Flucloxacillin/amoxicillin	8 (5.3%)		8 (2.7%)
Amoxicillin/flucloxacillin	6 (4.0%)		6 (2.0%)
Benzyl penicillin	6 (4.0%)		6 (2.0%)
Amoxicillin/clavulanic acid	4 (2.7%)		4(1.03%)
Cephalosporin	4 (2.7%)		4(1.3%)
Ampicillin	3 (2.0%)		3(1.0%)
Chloramphenicol	2(1.3%)		2 (0.7%)
Erythromycin	1 (0.7%)		1 (0.3%)
	151 (100%)	147(100%)	298(100%)

Table 4: Additional antibiotics

Second antibiotic	POPC	CCC	Total
Benzyl penicillin	13	1	14
Amoxicillin	1	8	9
Cotrimoxazole	0	5	5
Gentamycin	3	0	3
Amoxicillin/flucloxacillin	1	0	1
Ampicillin/cloxacillin	1	0	1
Benzathine penicillin	1	0	1
Tetracycline eye ointment	1	0	1
Total	21(100%)	14(100%)	35(100%)
Third antibiotic			
Gentamycin	3	1	4
Cotrimoxazole	2	0	2
Cephalosporin	1	0	1
Total	6(100%)	1(100%)	7(100%)

#### 4.2.1. Factors influencing cotrimoxazole prescribing

The key determinants of the decision to prescribe CTX were cadre, clinical setting, diagnosis, presenting complaint and HIV status are shown in Table 5 below.

**Table 5 : Factors influencing cotrimoxazole prescribing**

	Cotrimoxazole prescribed		Crude OR (95% CI)	Adjusted OR (95% CI)	P value
	Yes	No			
<b>Clinical setting, n = 29*</b>					
CCC	38 (20.6%)	1 (0.9%)	-	1.00	<0.001
POPC	146(79.4%)	114(99.1%)	-	0.001 (0.0001-0.03)	
<b>Diagnosis, n =* 216</b>					
URTI	21 (20.4%)	67(59.3%)	1.00	1.00	
GIT	17(16.5%)	3 (2.7%)	18.1(4.82-67.8)	3.1 (0.47-20)	0.242
Other	65 (63.1%)	43(38.5%)	4.82 (2.59-9.0)	1.3 (0.47-3.7)	0.616
<b>Cadre, n= 211</b>					
Clinical officer	49 (50.5%)	97(85.1%)	1.00	1.00	
Medical officer	41 (42.3%)	17(19.9%)	4.77 (2.46-9.25)	0.17(0.02-1.6)	0.120
Nurse	7 (7.2%)	0	-	-	-
<b>Clinical sign</b>					
Cough	31 (16.9%)	84 (73.0%)	0.07(0.04-0.13)	0.59(0.22-1.58)	0.292
Fever	16(8.7%)	33 (28.7%)	0.24(0.12-0.45)	0.92 (0.34-2.54)	0.880
Oiarrhoca	23(12.5%)	6(5.2%)	2.59(1.02 6.58)	12.86 (2.8-59.5)	0.001
<b>HIV status</b>					
Negative	38 (20.6%)	113(99.1%)	-	-	-
Positive	50 (21.2%)	1 (0.9%)	-	-	-
Unknown	96 (52.2%)	0	-	-	-

Cotrimoxazole was prescribed to 20.4% of the patients with URTI while GIT problems accounted for 16.5% of the indications. The clinical setting had a multiple fold influence on cotrimoxazole prescribing. It was more likely to be prescribed in CCC than in the POPC. Medical officers were more likely to prescribe cotrimoxazole. This could be due to the fact that most of die cotrimoxazole was prescribed in the CCC where most of the medical officers were based. Cotrimoxazole was 12 times more likely to be prescribed for diarrhoea adjusted OR (95%CI) 12.86. Patient routine cotrimoxazole prophylaxis and pneumonia accounted for 63.1% of the other diagnosis influencing cotrimoxazole prescribing.

#### 4.2.2: Factors influencing Amoxicillin prescribing

Amoxicillin was less likely to be prescribed by a medical officer, and was more most likely to be prescribed with a presenting complaint of cough (76.3%) and a diagnosis of a URTI, consistent with a report of the Specialist Advisory Committee on Antimicrobial Resistance (SACAR) Paediatric Subgroup [62]. It was also more likely to be prescribed to a HIV negative child with 82.9% of the prescriptions coming from HIV negative children. Patients who presented with a fever were 5 times more likely to receive amoxicillin OR 5.03 (95% CI:2.64-9.58) as the antibiotic of choice. Unlike cotrimoxazole, cadre did not affect prescribing of amoxicillin.

The various factors influencing the prescribing of Amoxicillin are shown in Table 6 below:

**Table 6: Factors influencing Amoxicillin Prescribing**

	Amoxicillin prescribed		OR (95% CI)	P value	Adjusted OR (95% CI)	P value
	Yes	No				
<b>Clinical setting</b>						
POPC	63(82.9%)	89(39.9%)	1.00	<0.001	1.00	
CCC	13(17.1%)	134(60.1%)	0.14(0.07-0.26)		0.69(0.28-1.72)	0.43
<b>Diagnosis</b>						
URT	50(68.5%)	38(26.6%)	1.00		1.00	
GIT	2(2.7%)	18(12.6%)	0.08(0.02-0.39)	0.001	0.30(0.04-2.19)	0.237
Other	21(28.8%)	87(60.8%)	0.18(0.1-0.35)	<0.001	0.32(0.15-0.69)	0.003
<b>Cadre</b>						
Clinical officer	56(76.7%)	90(65.2%)	1.00		-	
Medical officer	16(21.9%)	42(30.4%)	0.61(0.31-1.19)	0.148	-	
Nurse	1(1.4%)	6(4.4%)	0.27(0.03-2.28)	0.228	-	
sign						
Cough	58(76.3%)	57(25.6%)	0.07(0.04-0.13)	<0.001	1.00	
Fever	27(35.5%)	22(9.9%)	5.03(2.64-9.58)	<0.001	2.28(1.09-4.77)	0.028
Diarrhoea	4(5.3%)	25(11.2%)	0.44(0.15-1.31)	0.14	0.27(0.06-1.24)	0.094
<b>HIV status</b>						
Negative	63(82.9%)	88(39.6%)	1.00		1.00	
Positive	5(6.6%)	46(20.7%)	0.15(0.06-0.4)	<0.001	0.88(0.21-3.65)	0.866
Unknown	8(10.5%)	88(39.6%)	0.12(0.06-0.28)	<0.001		

Unlike cotrimoxazole, the prescribing of amoxicillin was not influenced by the clinical setting. The prescribing of amoxicillin for diarrhoea was not statistically significant unlike the prescribing of cotrimoxazole." Patients presenting with fever were 2 times more likely to receive a prescription for amoxicillin adjusted OR 2.28 (95% CI: 1.09-4.77) compared, to the ones that presented with just a cough. Patients with other diagnosis were 3 times less likely to receive amoxicillin compared to those diagnosed with URTI.

#### Irrational indications for Amoxicillin prescribing

Other diagnosis for which amoxicillin was prescribed accounted for 28.8% of the prescriptions. Amoxicillin was prescribed for conditions such as malaria, allergic reactions, chicken pox, mumps and bronchospasms that do not warrant an antibiotic according to the WHO guidelines. This is antibiotic misuse and increases the chances of development of resistance to antibiotics. For instance, mumps and chicken pox are viral infections and would not respond to an antibacterial drug.

### 4.3 Compliance to Guidelines on Management of Infections

#### 4.3.1 Overall compliance to guidelines

Only 57.2% of the antibiotics prescribed in both clinical settings were in compliance with the recommendation of the WHO Hospital Care for Children guidelines. Providers prescribed antibiotics for cough or other respiratory illness and no other serious symptoms, such as difficult or short breathing, even though such cases do not warrant an antibiotic according to the WHO guidelines. In the study done by Kenya Service Provision Assessment, 84% of the children who



presented with a cough and no other serious complications went home with an antibiotic prescription. In the same survey, the use of unwarranted antibiotics was common. Two thirds of children diagnosed with malaria were treated with antibiotics in addition to antimalarials [51]. This also compares to a study done in Botswana that found that 74% of antibiotic prescriptions were inappropriate. More than 70% of the cases had acute respiratory infections [56],

Th., overall compliance to guidelines is shown in Figure 2 below.

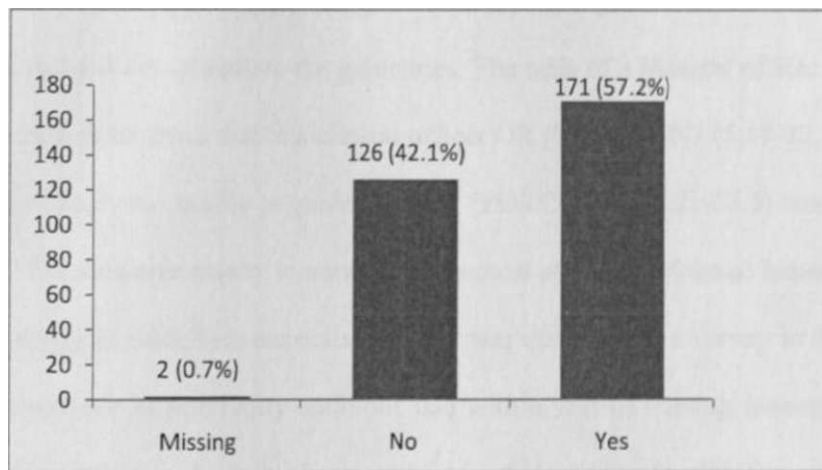


Figure 2: Overall compliance to guidelines

Compliance to guidelines was much better for the patients who were HIV positive. Prescriptions of HIV exposed/infected patients were 90 times more likely to comply to the guidelines crude OR 90.3 (95% CI:36.4-223.8), compared to those patients with without HIV.

There were differences in compliance to guidelines across different cadres. The influence of prescriber characteristics on guideline compliance is shown in Table 7 in the next page.

**Table 7: Prescriber characteristics and guideline compliance**

	(Guideline compliance		Odds ratio (95% CI)	P value
	Yes	No		
<b>Sex (n = 138)</b>				
<b>Female</b>	27 (47.4%)	43(53.1%)	1.0 (reference)	0.509
<b>Male</b>	30(52.6%)	38(46.9%)	1.26 (0.64-2.48)	
<b>Cadre (n = 211)</b>				
<b>Clinical officer</b>	38 (41.2%)	111 (88.8%)	1.0 (reference)	<0.001
<b>Medical officer</b>	44 (51.7%)	13(10.4%)	10.7(5.19-22.2)	
<b>Nurse</b>	6(7.1%)	1 (0.8%)	19.0 (2.21-63.5)	

\* Chi square test

Clinical officers were responsible for 88.8% of the prescriptions that did not comply to guidelines, followed by medical officers at 10.4%. Seventy six percent of the clinical officers prescribed drugs that did not comply to the guidelines. The odds of a Medical officer complying with the guidelines was 10 times that of a clinical officer OR (95% CI) 10.7 (5.19-22.2). A nurse was 19 times more likely to comply to guidelines OR (95% CI) 19.0 (2.21-63.5) compared to a clinical officer. This compares poorly to nurses and medical officers performed better with 22.8 and 14.3% complying to guidelines respectively. This was described in a survey in Atlanta that demonstrated an increase in familiarity antibiotic use with a year of training among paediatric residents. The same study found a lack of awareness of judicious use of antibiotics among lower cadre residents [57]. A similar study in Boston demonstrated that only 18% of primary care physicians reported to have profound familiarity with treatment guidelines. In this study self reported familiarity with guidelines was paradoxically associated with increased inappropriate antibiotic prescribing. Notably, it should not be assumed that guideline familiarity is associated with consistent guideline adherence [59].

Several studies have outlined models for possible reasons for non-adherence to guidelines among clinicians. Most models state that prescribers must be aware of the guidelines, agree with it,

adopt it as part of care in order to regularly follow the recommendations [63, 64, 65, 66]. This could partly be an explanation to high rate of guideline non-adherence among physicians.

#### 4.4 Prescription Errors

##### 4.4.1 Errors in prescribed dose per hotly weight and age

Ninety percent of the antibiotics on the POPC setting had the correct dosage per body weight and age. This compares poorly to the CCC setting with only 33.3% being correct as per the guidelines. This is worrying as it may lead to inadequate prophylaxis.

##### 4.4.2 Errors in the prescribed frequency and duration

A comparison of prescribing practices for HIV infected/exposed and non infected is shown in Table 8 below.

Table 8: Comparison of prescribing practices for HIV infected/ exposed children compared with non infected children

	<b>HIV infected/ exposed (n = 171) n (%)</b>	<b>HIV non infected (n = 126) n (%)</b>	<b>Crude OR (95% CI)</b>	<b>P</b>	<b>Adjusted OR* (95% CI)</b>	<b>P</b>
<b>Correct frequency</b>						
Yes	10 (68%)	136 (90.1%)	1.0 (reference)	<0.001	1.0 (reference)	0.002
No	47 (32%)	15 (9.9%)	4.29 (2.27-8.11)		3.88 (1.35-11.17)	
<b>Correct duration</b>						
Yes	138 (93.9%)	149 (98.7%)	1.0 (reference)	0.046	1.0 (reference)	0.31
No	9 (6.1%)	2 (1.3%)	4.89 (1.04-23.03)		3.27 (0.34-31.45)	
<b>Correct frequency and duration</b>						
Yes	100 (68%)	135 (88.8%)	1.0 (reference)	<0.001	1.0 (reference)	0.002
No	47 (32%)	17 (11.2%)	3.73 (2.02-6.88)		3.75 (1.33-10.57)	
<b>Correct dosage (per kg body weight)</b>						
Yes	49 (33.3%)	135 (90%)	1.0 (reference)	<0.001	1.0 (reference)	<0.001
No	98 (66.7%)	15 (10%)	18.26 (9.69-34.43)		16.85 (6.39-44.43)	

HIV non-infected children were more likely to receive correctly prescribed antibiotics. This is in regards to the correct dose per weight and age, correct frequency and correct duration as per the guidelines. HIV infected/exposed were 4 times more likely to receive antibiotics with the wrong frequency and duration, 4 times more likely to receive the wrong frequency and 16 times more likely to receive antibiotics with wrong dose as per body weight and age. While on the Other hand 88% of the antibiotic prescriptions surveyed had the correct frequency and duration among HIV non infected children compared to 68% of the HIV exposed/in fected. This could be because most of the prescribers and their training in the CCC concentrate on ARVs and they could possibly be overlooking 01 drug prescription accuracy.

Most of the prescribers prescribed the correct duration and frequency. The POPC setting appears to have had more prescriptions complying to the correct duration and frequency. It is worrying however that 20.8% of the prescriptions had the wrong frequency. This could lead to either over dosing or under dosing. Inappropriate antimicrobial dosing could lead to low efficacy of antimicrobial therapy and increase the chances of ADRs [67]. Optimizing the dose and duration of antimicrobial therapy could be used an effective tool and strategy to reduce antimicrobial resistance. Appropriate dosing provides patient- and pathogen-specific therapy and increases the potential to make antimicrobial therapy safer and more effective by accounting for factors such as renal function, underlying pathogen, and local patterns of resistance [68,69]

Consequences of wrong dosing have been demonstrated in studies showing a dose related toxicity profile particularly in children. A prolonged duration of use and a non- once daily use of antibiotics such as aminoglycosides has been associated with an increased tendency of nephro and irreversible ototoxicity in children and neonates [68,69,70].

The factors that determined the occurrence of prescription errors are shown in Table 9 below.

**Table 9:** Patient characteristics associated with prescribing practices in HIV infected/ exposed children and non infected children

	Correct frequency and duration for antimicrobials		Crude OR (95% CI)	P	Adjusted OR (95% CI)	P
	Yes (n = 235)	No (n = 64)				
Age in months, median (IQR)	15(8-32)	10(6-16)	NA	<b>0.0003*</b>	<b>1.0(1.01-1.07)</b>	0.01
Sex						
Female	104 (44.3%)	35 (55.6%)	1.00			
Male	131 (55.7%)	28 (44.4%)	1.57 (0.9-2.76)	<b>0.112</b>	<b>1.63(0.73-3.64)</b>	<b>0.231</b>
Diagnosis						
URTI	79 (43.4%)	9(26.5%)	1.00			
GIT	18(9.9%)	2 (5.9%)	1.02(0.2-5.2)	<b>0.976</b>	<b>4.44 (0.54-36.4)</b>	<b>0.165</b>
Other	85 (46.7%)	23 (67.7%)	0.42(0.2-0.96)	<b>0.041</b>	<b>0.42(0.14-1.27)</b>	<b>0.126</b>
HIV						
Non infected	135 (57.5%)	17(26.6%)	1.00			
HIV infected/ exposed	100(42.5%)	47 (73.4%)	0.27 (0.15-0.49)	<0.001	<b>0.27 (0.09-0.75)</b>	<b>&lt;0.013</b>
Pre-illation						
Cough	101(43%)	14(21.9%)	2.69(1.41-5.14)	<b>0.003</b>	<b>0.56(0.19-1.7)</b>	<b>0.301</b>
Fever	43(18.3%)	6(9.4%)	2.16(0.88-5.34)	<b>0.094</b>	<b>1.12(0.39-3.22)</b>	<b>0.827</b>
Diarrhoea	24(10.2%)	5(7.8%)	1.34(0.49-3.67)	0.566	0.16(0.03-0.81)	0.026
HIV AIDS status						
Negative	135(57.5%)	16(25.4%)	1.00			
Positive	44(18.7%)	7(11.1%)	0.74(0.29-1.93)	<b>0.544</b>	-	-
Unknown	56(23.8%)	40(63.5%)	0.17(0.09-0.32)	<b>&lt;0.001</b>	-	-
Sampling period						
Week 1	22(9.4%)	0(3.2%)				
Week 2	117(47.8%)	44 (69.8%)	1.00			
Week 3	96 (40.9%)	19(30.2%)	1.90(1.04-3.47)	<b>0.037</b>		
Clinical setting						
POPC	135(57.5%)	17(26.6%)	1.00			
CCC	100(42.6%)	47(73.4%)	0.28(0.15-0.49)	<0.001	0.27(0.09-0.75)	0.013
Cadre, n = 211						
CO	129(67.9%)	17(80.9%)	1.00			
MO	58(30.5%)	0	-			
Nurse	3(1.6%)	4(19.1%)	0.10(0.02-0.48)	<b>0.004</b>		

The odds of receiving a prescription with incorrect frequency and duration were 3 times more likely in CCC than in POPC; 6 times less likely for diarrhoea compared to other presentations.

The clinical presentation had a varying trend in the occurrence of prescribing errors. Figure 3 shows the influence of clinical presentation on occurrence of prescribing errors. Patients with cough (21.9%) had the prescriptions with the highest occurrence of errors, followed by fever (9.4%) and Diarrhoea (7.8%) respectively.

HIV infected patients had the prescriptions with the highest occurrence of errors with 73.4% of the patients having received prescriptions with the wrong frequency and duration. This compares poorly to the HIV non infected patients with about 26.6% of the prescriptions having errors.

Figure 4 below shows the influence of the HIV status on the occurrence of errors.

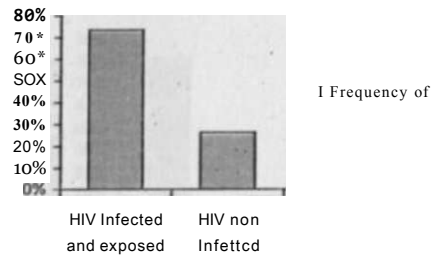
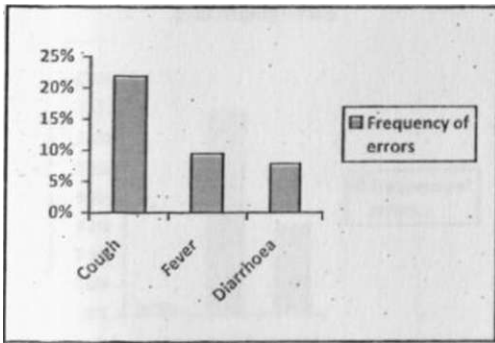


Figure 3: Influence of clinical presentation on clinical presentation on prescribing errors.

Figure 4: Influence of HIV status on prescribing errors

Week 2 of the sampling period had the highest occurrence of errors. Sixty-nine percent of the prescriptions sampled on week 2 had the highest occurrence of errors. This may be because of change of prescribers. Figure 5 in the next page shows the influence of the sampling period on the occurrence of errors.

Worthwhile to note, is the worrying trend of the influence of cadre on the occurrence of prescribing errors. Clinical officers were 10 times more likely to prescribe an antibiotic with the wrong frequency and duration compared to nurses. Eighty percent of the frequency and duration errors were made by clinical officers. Figure 6 below shows the influence of cadre on prescription errors.

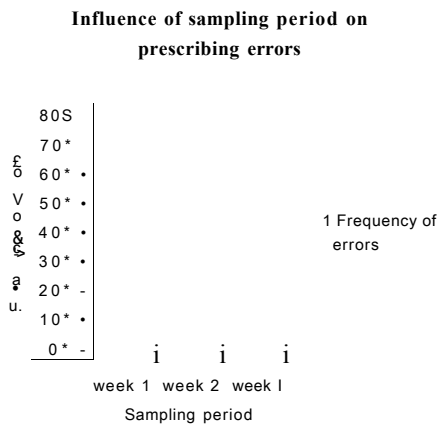


Figure 5: Influence of sampling period on prescribing errors.

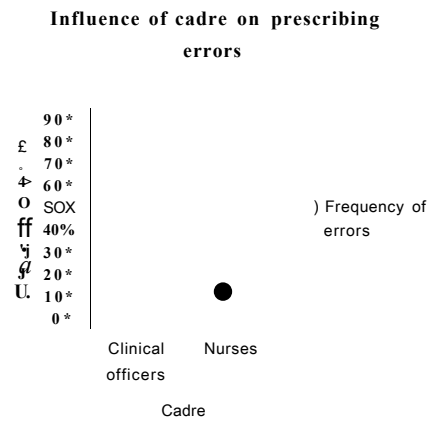


Figure 6 Influence of cadre on prescribing errors.

## **PART 2: QUALITATIVE STUDY OF FACTORS INFLUENCING PRESCRIBING**

### **4.5 Risk factors for inaccurate antibiotic prescriptions**

The irrational-antibiotic use was assessed using a qualitative study" by conduction six in-depth interviews with prescribers. I Medical OfTiccr, I medical Officer intern, I Nursing Officer, I Nursing Officer Intern, 1 Clinical Officer and 1 Clinical Pharmacist were interviewed.

#### **4.5.1 Social demographic information**

Each cadre in the medical profession was interviewed; one Medical officer, one medical officer intern, one clinical officer intern, one nursing officer intern, one nursing officer and a clinical phannacist.

The participants were chosen based on their roles in paediatric care in the hospital at the time of the study. They were chosen for the study purely based on their clinical role in drug therapy for children under five years at the time of the study. Three of the participants had over five years expericence in drug therapy in children while the remaining three had at least over six months experience.

The demographic profiles ofthe participants is shown in Table 10 in the next page.



Table 10: Demographic profiles of prescribers interviewed.

Health care profession	Years of experience
Clinical Pharmacist	7
Medical Officer	3
Medical Officer Intern	6-12 months
Nursing Officer	5 years
Nursing Officer Intern	6-12 months
Clinical Officer	6-12 months

#### 4.5.2 Role of bacterial infections in health status of children under 5 years in the facility

All the participants indicated that bacterial infections form the bulk of the reasons for admission of children under five years of age. However, majority of the participants felt that mild infections were more common than severe infections and that antibiotics play a major role in care and therapy of a child with a mild infection.

*"Like pneumonia, you must give an antibiotic, failure to which, the prognosis is poor. 10% will recover, 90% will die "* - Clinical Officer

According to the participants, the most common signs and symptoms that call for antibiotic prescriptions were fever, hotness of body, cough, crying a lot, poor feeding and febrile convulsions. Majority of the clinicians, felt that fever alone, would be a reason to prescribe an antibiotic.

*".....to start an antibiotic, you have to weigh a number of things. You have to take temperature. Temperature is an indicator of an infection. ...."*-Clinical Pharmacist

#### 4.5.3 Most commonly prescribed antibiotic

All the participants reported that Amoxicillin was the most frequently prescribed antibiotic in all clinical settings. Participants also reported co-trimoxazole, erythromycin and ciprofloxacin as other commonly prescribed antibiotics in the paediatric settings. Important to note, was also the reported common prescribing of injectable antibiotics like benzyl penicillin and gentamicin, followed closely by ceftriaxone.

*"In the ward the commonest is x-pen then gentamicin, and then once you don't respond to the first 2 we usually give ceftriaxone, then for meningitis we usually give x-pen and chloramphenicol as the first line, then if they are not responding within a duration of time maybe after 4 or 5 days you are not seeing the fever coming down then you now change to ceftriaxone. We have cases where we want to target the gram negative, we usually give ciprofloxacin, but in the outpatient, the commonest are amoxicillin, and maybe erythromycin and ciprofloxacin maybe can feature in the outpatient"- Medical Officer*

#### 4.5.4 Reasons for choice of antibiotic

Participants gave various reasons they would choose a particular antibiotic. There was a consistent reporting of confidence in the guideline even though most of participants gave other reasons for using an antibiotic other than what is given in the guidelines.

##### 4.5.4.1 Mothers' expectations

Participants reported that mother's expectations did not play a major role in their choice of antibiotic. However given a different setting, like the socio-economic status of the parent, some

of the participants reported that they would give in to the demands of the mother. Majority of the participants reported that they would prescribe an antibiotic demanded by a mother in a private hospital but not in a public hospital. One participant particularly cited this as a challenge to rational use of antibiotics.

*"...for the high class people it is unfortunate. It has led to that. Some mothers would want to get their child on Augmentin^ rather than Amoxit\* By the time they get like to two years, they can't even respond to Augmentin® itself. You have to give those things which are very expensive because you feel you want that thing to be hit hard." - Medical Officer*

#### 4.5.4.2 Cost and availability of drugs

The cost and availability of certain drugs appears to be a major determinant to choice of antibiotics. This is particularly so due to acute shortages and a narrow range of antibiotics available for choice. Most of the respondents felt that the most commonly prescribed drugs went out of stock frequently, leaving prescribers to prescribe what was available, even though it may not be the drug of choice or the indicated drug. When a particular drug was in plenty most of the prescribers reported that they were left with no option but to prescribe it, sometimes irrationally. This appears to be a major factor for irrational prescribing, common to all the respondents.

*"...depending on the availability of drugs. You see, ceftriaxone is very expensive and it goes out of stock every now and then. So you only have only one choice, that is x-penfbenzyl penicillin) and gentamicin." - Clinical Officer*

The essential drug list was cited by some respondents as narrow and forces most clinicians to stick to a narrow choice when it comes to choosing the right antibiotic for an indication.

Reportedly, consultants felt limited yet their scope is beyond the essential drug list. The drugs supplied by the regular supply chain appeared to be inefficient and did not cover a wide spectrum of treatment. The supply chain was also quoted as inconsistent and unreliable with some consignments bearing short expiry drugs forcing the "push" system on the patients.

*"...we have a problem. Whenever there's a consultant, you cannot limit him to the essential drug list, that's a big problem because they normally provide us with simple drugs. . . . . The drugs provided by KEMSA don't cover the whole spectrum of the treatment we require. Like here we have a lot of problems- the consultant wants a particular drug, and he needs it and it 'i not in the essential drug list, some just simple ones but they are very important. So the drug provision of KEMSA in terms of coverage of spectrum is very poor. And then there is unavailability of the drugs, like since I came here, I've not seen them bring drugs properly. They supply you like one day they supply you with drugs which can fill in a store one time there's none, or the next time, it's short expiry then next time we don't ave that drug completely. And that's the major influencing factor , the dnigs have to be available. There are hundred? of antibiotics, but the major ones need to be there, so the few ones which are not there you can say now this one can replace this one"- Clinical Pharmacist*

This was reported across all the cadres. Majority of the respondents reported that most of the time, they prescribed whatever was available in the hospital, and were majorly guided by the perceived social history and status of the patient.

*"....most of the drugs are not available in our hospital. For example you find a patient with an infection which you think there are certain bacteria, there are certain drugs which will help the patient and you don't have it. For example staphylococcus aureas is only cured by Floxapen® , but the hospital doesn "t have that drug. So you end up giving Amoxil\* , because you look (at) the*

*patient, doesn't afford the drug, doesn't even have money to buy a card for 20 shillings... So what do you do, you can't just be giving them money. So you just give any drug that is available and you pray to God ..."- Clinical Officer*

The cost of some antibiotics was also reported as a barrier to rational prescribing, with some being too expensive for public hospitals to procure independently and at the same time unaffordable to the patient. Some prescribers reported that they would rather prescribe a cheaper or affordable antibiotic and be sure that the patient would afford than prescribe an expensive antibiotic which the patient would find difficult to buy.

#### 4.5.4.3 Past experience

The side effects of some drugs was reported as a past experience by all the respondents that would make one veer away from a certain drug in future.

*'On one occasion there was a patient who had meningitis and they were using Cefogram\* for a long long time and the temperatures were still very high. So I spoke to the MO interns (and told them) we need to change this drug, there's a better drug called Chloramphenicol which penetrates the meninges very well. The side effects are there. But now we have to weigh the side effects versus the benefits. We'll change this Cefogram\* and put chloramphenicol". Then they refused and said, once you use these high drugs of the highest level, you cannot use these other ones "- Clinical Pharmacist*

Near death and sometimes fatal experiences was reported by some respondents as a reason one would choose not to prescribe the same drug to a patient fearing that the experience might recur.

*"Because maybe you could have given a drug then it causes severe side effects. Like I have a patient I gave Eso-kit Then all of a sudden the patient came back after 3 days with severe*

*rashes (that were) pus-like. I had not asked if the patient has any allergies to clarithromycin. And you know it has that skin eruption.."- Clinical Officer*

#### 4.5.4.4 Practices of peers

Senior and more experienced peers were reported by all the respondents to be the most consulted colleagues for the appropriate choice of antibiotic. Most of the respondents reported that they were most likely to consult colleagues when trying to choose whether to change an antibiotic or choose one over the other. Prescribers from lower cadres felt that they were better off referring the patient to a senior cadre rather than make the decision themselves.

*"Colleagues also affect you because you will kind of approach that antibiotic with a 50-50 mind. You will not want to treat a child then 5 days later they are not improving you will want to just see immediate effects and if this friend of your has had an experience you 'II want to go for it. " - Medical Officer*

*"As an intern...we are not allowed to make a diagnosis, we refer them to the Medical Officers, the (he) makes the diagnosis, they send them to the nurse for the test, so by the time they reach to us, we are giving them advice on how to take care of themselves post diagnosis."- Nursing Officer Intern.*

#### 4.5.4.5 Use of guidelines

All the participants reported that they are aware of the existence of guidelines for reference when prescribing antibiotics to children. Interestingly, only the lower cadres (interns and clinical officers) reported that they referred to the guideline each time they prescribed an antibiotic. On guideline change, participants reported that they learnt about changes from colleagues who

attend trainings more regularly. The PMTCT guidelines were reported to be the most referred to guideline.

*"The guidelines we have is the latest. And we have a "sister"(nurse) who has gone for the course. I was just updated by the "sister " who went for the course even the other health workers who are there.... In case am not understanding whatever the case of a patient, /just call her (the nurse) because she is trained and is up to date and is familiar with everything, she attends all the meetings, she meets with the dasco and all that."- Nursing Officer*

However, it was interesting to note that some participants felt that it was not necessary to refer to the guidelines all the time. One participant reported that, noteworthy, most doctors tend to use "stronger" antibiotics with the intention to "hit hard" and this leads to irrational antibiotic prescribing.

*"... as doctors sometimes we tend to be over ambitious, that's the commonest challenge. Hut I believe it's better to be over ambitious than under. That means we tend to give strong antibiotics more often, you 'll tend to give a "higher" one than giving the lesser one.... my feeling is because you feel like you want to hit the infection once and for all. " -Medical Officer*

#### 4.5.4.6 Poor Laboratory networking

Improper laboratory networks were reported as a barrier to rational and appropriate choice of antibiotics in the study area. Inaccurate and delayed results were cited as among the major barriers and problems encountered. This was reported by all the cadres.

*"Actually there is improper lab working. Someone can do differentials, and then the lab works do something different, you treat pneumonia and then it turns out to be something else. So lab works sometimes is not precise."* -Clinical Pharmacist

Most participants reported that culture and sensitivity tests would reduce emergence of antibiotic resistance because then prescribers would prescribe targeting a particular organism making therapy more effective.

*"if you've done the culture then you'd be able to know which organism you are dealing with and after that you 'll be able to know which antibiotic this organism is responding to then you 'll be able to target straightforward without galloping in the dark."* - Medical Officer

#### **4.5.4.7 Work load**

Majority of the participants reported that on days they felt overworked; they tended to give prescriptions which may have errors. Health workers tend to work mechanically just to get the "job done" or clear the queue and may at times fail to listen to the client and hence end up with a wrong diagnosis, hence the wrong choice of drug.

*"...like in our set up here, you find that you are in the outpatient working half day, like six hours or 8 hours and you have a queue of like 70 kids. So sometimes you'll forget sometimes you get tired of listening to all the questions you might end up giving the wrong drug, the wrong prescription maybe you just give paracetamol, Piriton , because of the wrong factors.."*

Clinical Officer

#### **4.5.4.8 Influence of HIV status of patient and Medication History**

Majority of the participants reported that they would prescribe a different range of antibiotics for a HIV positive child who presented with similar complaints to that of a HIV negative child. One



participant reported that HIV patients were more prone to getting infections and there was a higher probability of them having been on many antibiotics before and would therefore not respond to first line antibiotics. In most cases, participants reported that the HIV status would make them to choose a range of different antibiotics.

*"...once you are immunocompromised then you are exposed to myriads of infections so then the infections can progress very fast. That way, you will need a strong antibiotic. So it also indicates because you are immunosuppressed it's only the drugs which help you to fight. The immunity of your body is gone. So you need to step the dose (up) and use a strong antibiotic"* Clinical Pharmacist

Previous non-prescription use of antibiotics was reported by majority of the participants as factor that would determine the choice of antibiotic to prescribe. Most of the participants reported they always asked medication related questions to mothers before prescribing antibiotics. Previous use of an antibiotics, during the current illness, would mean that patient would fail to respond to the same drug if put on it. A positive response from the mother would call for a different choice of antibiotic other than the recommended one.

*"..you want to know whether there is resistance to a certain drug so you first ask whether they had previously taken the child to a hospital or whether they had prescribed the drug themselves, because most of them do that, they go to the chemist and ask for AmoxilParacetamol. So if this child has used AmoxiP for like 5 days basically you would not give Amoxit<sup>s</sup>"* - Clinical Officer

*"...not the HIV status alone, the history also... they have had several bouts of pneumonia before and this one has just come with pneumonia today and is immunocompetent. I'll consider giving (the HIV positive) a stronger antibiotic."* Medical officer

#### 4.5.4.9 Influence of **Cadre and qualification**

The lower cadres felt they were lesser qualified to make proper diagnosis and prescribe correctly.

This was mostly reported by the nurses, who felt they were not properly equipped and oriented to

be prescribing to patients. Unfamiliarity with drugs was reported to be among the major challenges that they faced while prescribing.

*"If the mother comes and complains that my baby is having fever, we are supposed to take the temperature, but ourselves we have no thermometer, so we just check the fore head, and you understand that the baby is having fever... we don't write the dose because sometimes we have a paper which says the baby from this age should take this much but am not conversant with HIV drugs am not trained about them. If it is not there I just write then the pharmacist will just explain to the mother and write the right dose. "- Nursing Officer*

#### **4.6 Comparison of prescribing practices and in depth interview**

The World Health Organization (WHO) estimates that more than half of all medicines are either prescribed or dispensed inappropriately [6]. Similarly, only slightly more than 50% of the antibiotics prescribed in this study complied with the recommendations of the WHO guidelines. From the qualitative study, it is clear that the prescribing of antibiotics is influenced by several factors. The narrow range of drugs prescribed in the hospital is influenced by the availability of drugs and the narrow range of drugs to choose from in the formulary. Failure to provide available, safe and effective drugs is often an impetus for irrational drug use [4]. This finding was consistent in this study as most prescribers reported that their prescribing trends were guided and skewed towards the available antibiotics.

However, it is interesting to note from literature there has been an increasingly worrying trend of increase in resistance to commonly prescribed antibiotics. Studies from various countries in Africa, have demonstrated striking resistance rates of highly prescribed and consumed antibiotics [24, 25]. Furthermore, the overconsumption of chemically and pharmacologically related antibiotics has significantly increased cross resistance. This underscores the need for interventions like formulation of antibiotic policies, education and training of health care workers on the appropriate use of antibiotics to reduce the development of resistance. Inappropriate antimicrobial use by patients with true bacterial infections has also been linked and associated with treatment failure and masking of the underlying clinical symptoms [26].

As seen in the survey of prescribing practices, nurses were more likely to prescribe prescriptions with dosage errors. This also comes out as a risk factor in the in depth interview as nurses reported not to be confident with doses of most drugs. Nurses and interns also feel less confident to deal with complicated cases and would rather refer to a senior clinician. Previous studies have also similarly demonstrated incorrect duration of antibiotics with notably wrong dosing trends particularly in children [20,46].

The cost and availability of drugs could be the reason for the overprescribing of amoxicillin and cotrimoxazole seen in both clinical settings. These two drugs are known to be frequently available and of low cost in the study setting. They are also perceived to have few side effects, hence safer for children. There was a worrying irrational prescribing trend of amoxicillin in the study site. This somewhat ties in with previous audits on antibiotic use in hospitalized patients

which have demonstrated similarly high proportion of patients with antibiotic prescriptions with unclear indications [47].

Respiratory tract infections are a frequent cause of medical consultations among children under 5 years. This has resulted in widespread use of antibiotics, and is a major factor that drives the emergence of antibiotic resistance [10]. This was also a consistent finding in this study. As seen in the survey of prescribing practices, most patients who presented with URTI and fever in both clinical settings received an antibiotic prescription. This also comes out as a theme in the in depth interviews as all the participants reported that fever alone was an indication of an infection and would warrant an antibiotic. Respondents also reported the presentation of a cough in a child, as another reason for prescribing an antibiotic.

Most clinicians feel that HIV positive children deserve to get "stronger" antibiotics than HIV negative children. Reportedly, HIV positive children are perceived to suffer from more infections and may therefore have been exposed to more antibiotics rendering them resistant. The use of unnecessarily expensive drugs such as, third generation, broad spectrum antimicrobial drugs when a first line, narrow spectrum agent is indicated is an example of inappropriate drug selection [4]. This is the most likely outcome in the study setting if one was to consider the results from the in depth interview with the reported belief that HIV positive children should get "stronger" antibiotics. On the contrary, this was not the outcome seen from the survey of prescribing practices where HIV positive children were actually noted to be receiving a narrower range of antibiotics.

Prescriptions for HIV exposed/infected children were more likely to comply with the World Health Organization Guidelines for choice of antibiotics compared to the HIV non infected children. However, HIV exposed/infected children were also more likely to receive antibiotic

prescriptions with the wrong dose. This could significantly lead to ineffective prophylaxis and management of opportunistic infections. From literature, paediatric dose adjustment continues to be a major issue of concern and particularly so in HIV settings, Kenya being one of them.

Amoxicillin was the most commonly prescribed antibiotic and also the most irrationally prescribed in both clinical settings. This was mostly associated with the lower cadres of health workers. Amoxicillin was prescribed for conditions such as malaria, allergic reactions, chicken pox, mumps and bronchospasm that do not warrant an antibiotic according to the WHO guidelines. This is antibiotic misuse and increases the chances of development of resistance to antibiotics.

## CONCLUSION

Prescriptions for HIV exposed/infected children were more likely to comply with the World Health Organization Guidelines for choice of antibiotics compared to the HIV non infected children. However, HIV exposed/infected children were-also more likely to receive antibiotic prescriptions with the wrong dose. This could significantly lead to ineffective prophylaxis and management of opportunistic infections. Amoxicillin was the most commonly prescribed antibiotic and also the most irrationally prescribed in both clinical settings. This was mostly associated with the lower cadres of health workers.

There was a much wider range of antibiotics prescribed among the non-HIV infected children as compared to the HIV infected. The most commonly prescribed antibiotic for the HIV infected patients was cotrimoxazole while for the HIV non infected, amoxicillin was the most prescribed.

Majority of the prescribers felt that unavailability of the right antibiotics forced them to prescribe irrational antibiotics. Nurses who prescribe to HIV exposed children reported they were not well equipped to prescribe correctly and did not know the doses of most of the antibiotics prescribed in the Comprehensive Care Clinic. Lack of proper laboratory networks, heavy work load, perceived financial status of the patient and side effects were some of the risk factors reported for wrong/irrational antibiotic prescribing.

## **RECOMMENDATIONS**

Pharmacy staff should also be sensitized on dose adjustment and should be encouraged to work with prescribers where an error is noted. This shows an indication for the need to introduce a Clinical Pharmacist with Paediatric specialization, at the study site, in order to step in the gap for specialized and appropriate pharmaceutical care interventions.

Amoxicillin is probably over used because it is the only safe and cost effective drug available in most public hospitals in Kenya. This could be minimized by increasing the range of antibiotics in the national formulary. Targeted interventions for prevention of overuse, such Continuous Medical Education could be initiated within a period not less than 24 months from the date of conclusion of this study.

More health workers need to be sensitized on the use of the World Health Organization Guidelines while prescribing antibiotics. A clinical pharmacy team would be best suited for this intervention.

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## **FUNDING INFORMATION**

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## APPENDICES

### Appendix A: Work Plan

Activity description	Time Period											Expected output/Outcome	Resources requirements
	J	F	M	A	M	J	J	A	S	O			
Months of the year	J	F	M	A	M	J	J	A	S	O			
Proposal development	X	X	X	X								Approved proposal	Finances, skills and manpower
Data collection						X	X					Collected data	Finances, skilled manpower
Data entry and analysis									X			Fully Analyzed data	Finances, skilled manpower
Thesis defense										X		Completed thesis	Skilled manpower

### Appendix B: Budget by Activity

S.no.	Cost Item	Cost Units	No. of Days	Unit Cost (KES)	Costing	Total (KES)
1	Preparations Phase					
	a) Stationary (Notebooks, pens, printing of questionnaires)	1	1	2000	1*1*2000	2000
	b) Transport	1 principal investigator	2	500	1*2*500	1000
	c) Communication	1 principal investigator	2	250	1*2*250	500
	d) Finalization of concept paper	1 principal investigator	1	2000	1*1*2000	2000
	i) Sub-total					5500
2	Implementation Phase: Situation Analysis Survey					
	i) At the start of the program					
	a) Site visit for data verification (transport, communication, and out of pocket)	1 principal investigator	1	3000	1*1*3000	3000
	b) Project proposal development	1 principal investigator	3	1000	1*3*1000	3000
	c) Accommodation for principal investigators	1 principal investigator	30	1500	1*30*1500	45,000
	d) Incidentals for principle investigators	1 principal investigator	30	500	1*30*500	15,000
	e) Transport and communication	1 principal investigator	30	500	1*30*500	15,000
	f) Bio-statistician data analysis fee	1	30	500	1*30*500	10,000
	i) - Sub-total					91,000
	Total Cost					96,500

Appendix C: KNH/UoN KRC Approval



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Ref. KNHERC/A't17

16- May 2012

Ngun Josephine Wambui  
 U59,63613/2010  
 School of Pharmacy

University of Nairobi

Dear Josephine

Restarch proposal: Comparative study of antimicrobial use In HIV Infect\*d/oxposed and non infected children at Nalvasha District Hospital. Kenya" (P68/02/2012).

Tula ii to inform you that the KNH/UoNEthics K .Research Committee (ERC) hits rewiowcfi and approved your above revised rosoarch proposal The approval periods are 16' May 2012 to 15 ' May 2013

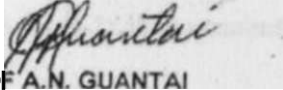
This approval n subject tc compliance win the fof.owing raqursmonts

- a) Only approved documents - informed cnser-ts study instruments advertising matenals etc, will be used
- b) Ail changes (amendments deviations /oiaiiions etc. are submitted for review and approval by KNH/UoN cRC before implementation
- c) Death and life threatening problems ard severe adverse ovents (SAEs) or u -enpected adverse events whetfier related or unrelated to tne study must be reported to tho KNH/UoN ERC witnm 72 hours of notification
- d) Any chaoges anticipated or otherwise that may ncrease the risks or affect safety or welfare of study participants and others or affect tne ntegoty of tte research must b« roporteo to KNHAJoN ERC within 72 hours
- e) Submission of a request for renewal c/ approval at least 90 days pnor to expiry of the approval penod (Attach a comprenonsM) oroaroMs razor; to tuooort iho ntnowolt
- f) Clearance for export of biological specifiers must be obtained from KMH LoN Elites S Research Committee for each batch of shipment
- g) Submission of an uxocuitvu summary -oport within 90 days upon complete" of the study This information will form part ol the data base that will bc consulted in hjtu-e when processing related research studes so as to minimize cnarces of study duplication and/or pftqurimn

*"Protect to Discover*

For more details consult the KNH/UoN -ERC website [www.uonbi.ac.ke/actiyities/KNHUoN](http://www.uonbi.ac.ke/actiyities/KNHUoN)

Yours sincerely



**PROF A.N. GUANTAI**  
**SECRETARY, KNH/UON-ERC**

- ex.     **The Deputy Director CS. KNH**  
          **The Principal, College of Health Sciences. UON**  
          **The Dean, School of Pharmacy. UON**  
          **The HOD, Records, KNH**  
          **Supervisors. Dr. Faith Okalebo. Dr. Evans Mwangangi. Dr Shital Maru**

*"Protect to Discover"*

## **Appendix D): IMCI and PMTCT guidelines for antibiotic use in children in HIV settings**

### **Appendix D-1; Management of pneumonia in HIV exposed and infected children**

#### **1. Co-trimoxazole (Trimethoprim/Sulphamethoxazole combination) High Dose**

- In settings where HIV prevalence is high, and therefore PCP a most likely cause of pneumonia, only infants who present with features of severe and very severe pneumonia should be given Cotrimoxazole, the empiric treatment for PCP. Cotrimoxazole should not be used for treatment of pneumonia in children older than 12 months, as the chances of severe pneumonia being due to PCP is very small.

The dose is trimethoprim 5 mg/kg and sulphamethoxazole 25 mg/kg 4 times per day by mouth; minimum duration 21 days;

If IV route is chosen, 15 mg/kg/day of trimethoprim and 75 mg/kg/day sulphamethoxazole is recommended.

If there is a severe drug reaction or a history of severe drug reaction to sulphamethoxazole, give TMP 5 mg/kg/dose, 4 times per day PO + Dapsone 100 mg/day PO x 21 days.

#### **2. CTX Prophylaxis**

CTX prophylaxis should be given to:

- All HIV-exposed from 6 weeks age and should be continued until the HIV infection is confirmed to be absent.
- All HIV-infected children
- Children with a history of PCP
- Children with severe immunosuppression based on CD4.

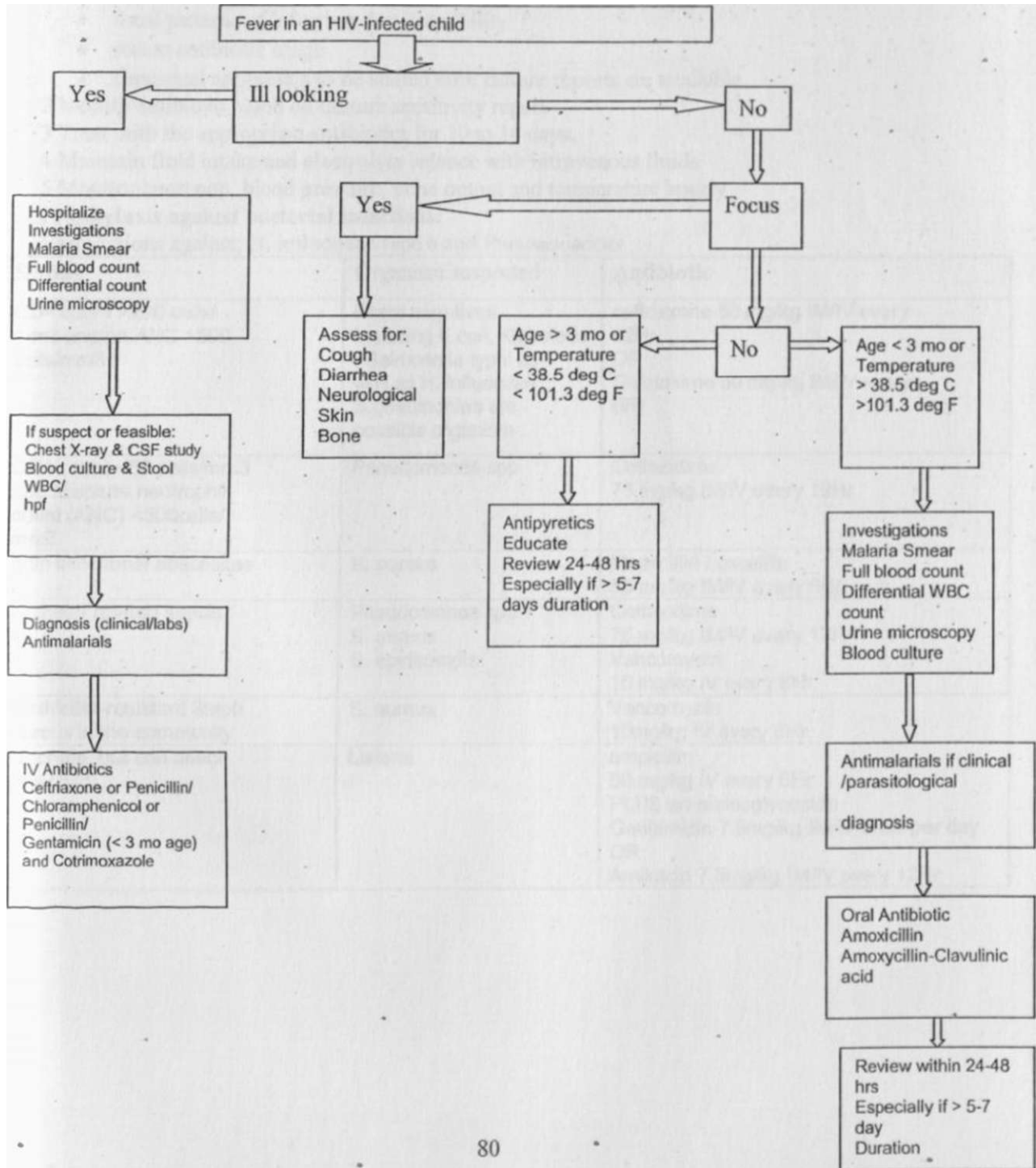
The CTX prophylaxis dose is based on a standard Trimethoprim dose of 6-8 mg/kg/day once a day.

**Appendix 1/1: Diarrhoea and other gastrointestinal problems in HIV-infected children**

For diarrhoea with blood:

**Ciprofloxacin (15 mg/kg, 2 times/day for 3 days), OR Pivmecillinam (20 mg/kg, 4 times/day for 5 days), OR Ceftriaxone (50-100 mg/kg, once a day IM for 2-5 days), AND Metronidazole (7.5 mg/kg 3 times a day for 7 days)**

**Appendix D-3: Fever in the HIV-infected child**



## Appendix 1)-4: Sepsis in Children

### Treatment:

1 Antibiotics are started based on:

- local patterns of infection & susceptibility
- recent antibiotic usage
- Empirical antibiotics to be started until culture reports are available.

2 Modify antibiotic based on culture sensitivity report

3 Treat with the appropriate antibiotics for 10 to 14 days.

4 Maintain fluid intake and electrolyte balance with intravenous fluids

5 Monitor heart rate, blood pressure, urine output and temperature hourly

Prophylaxis against bacterial infections:

Setting	Organism suspected	Antibiotic
CD4 count >200 cells/mm <sup>3</sup> and an ANC >500 cells/mm <sup>3</sup>	Gram negatives including E.coli, Klebsiella, Salmonella typhi as well as H. influenzae, S.pneumoniae are possible organism	ceftriaxone 50 mg/kg IM/IV every 12Hr OR Cefotaxime 50 mg/kg IM/IV every 6Hr
CD4 count <50 cells/mm <sup>3</sup> and absolute neutrophil count (ANC) <500cells/mm <sup>3</sup>	Pseudomonas spp	Ceftazidime 75 mg/kg IM/IV every 12Hr
Skin infections/ abscesses	S. aureus	Methicillin / oxacillin 50 mg/kg IM/IV every 6Hr
Catheter related sepsis	Pseudomonas spp S. aureus S. epidermidis	Ceftazidime 75 mg/kg IM/IV every 12Hr Vancomycin 10 mg/kg IV every 8Hr
Methicillin-resistant Staph aureus in the community	S. aureus	Vancomycin 10mg/kg IV every 8Hr
Neonate, but can affect any child	Listeria	ampicillin 50 mg/kg IV every 6Hr PLUS an aminoglycoside Gentamicin 7.5mg/kg IM/IV once per day OR Amikacin 7.5mg/kg IM/IV every 12Hr



**Appendix D-5: Dose of CTX OI prophylaxis**

<b>Weight of Child (kg)</b>	<b>CTX tablets 20 mg TMP/100 mg SMX pediatric strength (120 mg)</b>	<b>Cotrimoxazole suspension 40 mg TMP/200mg SMX/ 5ml (240 mg)</b>	<b>CTX tablets 80 mg TMP/400 mg SMX regular strength (480 mg)</b>	<b>CTX Tablets 160 mg TMP/800 mg SMX Double; strength (960 mg)</b>
1 -4	1 tab	2.5 ml	1/2 tab	-
5-8	2 tabs	5 ml	1/2 tab	1/2 tab
9-16		10 ml	1 tab	1/2 tab
17-50			2 tabs	1 tab
>50			2 tabs	1 tab

**Prophylaxis against Pneumocystis jiroveci Pneumonia (PCP) in children where Cotrimoxazole is contraindicated**

Alternative drugs to use if CTX is contraindicated are given below:

A second choice would be either Dapsone or atovaquone

**Dapsone**

- Children > 1 month: 2 mg/kg/24 hours orally once daily,
- if both CTX and Dapsone are contraindicated (e.g., in children with G6PD deficiency who get haemolysis with CTX and Dapsone), then use either:

**Atovaquone**

- 30mg/kg/day for age 1-3 months
- Higher dose 45mg/kg/day for age 4-24 months

OR

**Aerosolized Pentamidine**

- Q300 mg in 6 ml water via inhalation nebulizer once monthly
- Children > 5 years



Appendix E: Data collection form

Case number:.....Clinical setting

Date\_

**A. Demographic characteristics of patients:**

Age (in months)

Sex: Male [ ] Female [ ]

Place of residence

HIV/AIDS exposure Yes [ ] No [ ] Unknown [ ]

HIV/AIDS status positive [ ] Negative [ ] Unknown [ ]

**B. Demographic traits of mother/guardian**

Age Sex.....

Residence.....HIV status

Level of education

Occupation

Is child on HAART Yes [ ] No [ ]

If yes which regimen?

**C. Diagnosis**

Chief

complaint

Diagnosis: URTI [ ] UTI [ ] GIT [ ] Other(Specify)

Investigation(s)

done:

Concurrent conditions (if any)

**I). Antibiotics prescribed**

Antibiotic	Dose	Route of Admn	Frequency	Dose as per weight/age	Complies with guidelincs(Y/N)

**K. Prescriber information**

Cadre:

Gender

## Appendix F: Glide for in depth interview for prescribers

1. **Introduction:** My name is Dr Josephine Wambui. I am doing a study on antibiotic use in Children.

### 2. Purpose of interview:

I know that antibiotics are probably the most commonly prescribed drugs in our setup. I am interested in knowing your views about antibiotic use and prescribing. It would be very useful if we could spend some time together to discuss this issue.

### 3. General background:

Could you please tell me what your position is in this clinic and for how long you have worked here?

### 4. Interview topics:

#### Clinical Experience

Can we talk for a while about your work in the clinic? How many patients do you treat in an average day and what kind of problems do they have?

*Probe - number of patients under 5 years of age*

- *subjective prevalence of bacterial infections*
- *importance of bacterial infections in under-fives*

#### Diagnosis

I would like to talk more about acute bacterial infections in children. Could you please tell me how acute bacterial infections usually present themselves in children in this community?

*Probe: • Key signs and symptoms*

*Different forms of presentation*

*Subjective organization of diagnoses*

- *Relative prevalence of severe vs mild bacterial infections*

How do you know that a child has a serious bacterial infection?

*Probe: - Key history questions*

- *Physical examinations performed*
- *Importance of lab examination*

#### Treatment

How do you usually treat a child who has a mild bacterial infection?

*Probe: - Number of drugs prescribed for typical cases*

*Name of specific drugs prescribed*

*Use of injections*

*When is treatment varied*

*Treatment of severe v.? mild bacterial infection*

### **Use of antibiotics**

I would like to talk some more about the use of antibiotics in treating bacterial infections in different children. What factors determine whether you give an antibiotic or not?

*Probe; - Influence of personal experience*

*Mothers expectation*

*- Practices of peers*

*- Essential drug list*

*Previous/recent use of non-prescription antibiotics*

*- Knowledge of standard treatment guidelines*

*- Any challenges that one might face*

### **Implication of HIV status**

Does the HIV status of a child influence the choice of antibiotic?

*Probe: - choice of antibiotic in HIV*

*- Reason for choice of antibiotic*

*Influence of availability/non-availability*

### **5. Wrap-up**

Thank you for your time and willingness to participate in this study.

Do you have anything to add to what was already discussed or were there important topics which were not covered?

*Probe: - Use of antibiotics*

*Treatment of bacterial infections*

## **Appendix G: Consent form for in depth interview with prescribers**

To be read in a language that the respondent is fluent in.

**Title of the study:** Comparative study of antimicrobial use in HIV infected/exposed and non-infected children at Naivasha District Hospital.

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

**Investigator:** Dr Nguri Josephine Wambui, P.O BOX, 30197-00400, Nairobi.

**Supervisors:** Dr F.A Okalebo, department of Pharmacology and Pharmacognosy; Dr Shital Maru, Department of Pharmaceutics and Pharmacy Practice, Dr E.M Mwangangi, Department of Pharmaceutics and Pharmacy Practice.

**Ethical Approval:** Kenyatta National Hospital/ University of Nairobi Ethical and Research Committee, P.O BOX 20723-00100, Nairobi. Tel 2726300/2716450 Ext 44102

Permission is requested from you to enroll in this medical research study. You should understand the following general principles which apply to all participants in a medical research:

- i. Your agreement to participate in this study is voluntary.
- ii. You may withdraw from the study at any time without necessarily giving a reason for your withdrawal.
- iii. After you have read the explanation please feel free to ask any questions that will enable you to understand clearly the nature of the study.

**Introduction:** In this study I am assessing the use of antibiotics among HIV exposed/infected and non-HIV infected children less than 5 years of age.

**Purpose of the study:** The purpose of the study is to compare antibiotic use and to identify the prescriber related risk factors for irrational antibiotic use/prescribing, in both HIV exposed/infected and non HIV infected children.

**Procedure to be followed:** With your permission, I will engage in a discussion about antibiotic prescribing which I will record using a voice recorder. I will also take some notes on pen and paper where necessary. All information obtained will be handled with confidentiality.

**Risks:** There will be no risks involved in this study.

Benefits: There will be no direct benefits to you but the findings will be useful in improving the quality of antibiotic prescribing among children less than 5 years.

Assurance of confidentiality: All information obtained from you will be kept in confidence. At no point will your name be mentioned or used during data handling or in any resulting publications. Codes will be used instead.

Contacts: In case you need to contact me, my academic department or the Kenyatta National Hospital/ University of Nairobi Ethics and Research Committee concerning this study please feel free (o use the contacts provided above.

I now request you to sign the consent form attached.

CONSENT FORM

**A COMPARATIVE STUDY OF ANTIMICROBIAL USE IN HIV INFECTED/EXPOSED AND NON INFECTED CHILDREN AT NAIVASHA DISTRICT HOSPITAL, KENYA**

I \_\_\_\_\_ give consent to the investigators to interview me and use the information obtained in her study. The nature of the study has been explained to me by Dr. Nguri Josephine.

I confirm that I have explained the nature and effect of the study.

Signature \_\_\_\_\_

Date—



## **Appendix H: Consent form for survey of prescribing practices**

To be read in a language that the respondent is fluent in.

**Title of the study:** Comparative study of antimicrobial use in HIV infected/exposed and non-infected children at Naivasha District Hospital.

**institution:** Department of Pharmaceutics and Pharmacy Practice, School of Pharmacy, University of Nairobi, P.O BOX 30197-00400, Nairobi.

**Investigator:** Dr Nguri Josephine Wambui, P.O BOX, 30197-00400, Nairobi.

**Supervisors:** Dr F.A Okalebo, department of Pharmacology and Pharmacognosy; Dr Shital Maru, Department of Pharmaceutics and Pharmacy Practice, Dr E M Mwangangi, Department of Pharmaceutics and Pharmacy Practice.

**Ethical Approval:** Kenyatta National Hospital/ University of Nairobi Ethical and Research Committee, P.O BOX 20723-00100, Nairobi. Tel 2726300/2716450 Ext 44102

Permission is requested from you to enroll in this medical research study. You should understand the following general principles which apply to all participants in a medical research:

- i. Your agreement to participate in this study is voluntary.
- ii. You may withdraw from the study at any time without necessarily giving a reason for your withdrawal.
- iii. After you have read the explanation please feel free to ask any questions that will enable you to understand clearly the nature of the study.

**Introduction:** In this study I am assessing the use of antibiotics among HIV exposed/infected and non-HIV infected children under 5 years of age.

**Purpose of the study:** The purpose of the study is to compare antibiotic use and to identify the prescriber related risk factors for irrational antibiotic use/prescribing, in both HIV exposed/infected and non HIV infected children.

**Procedure to be followed:** With your permission, I will use your child's file to obtain some information on your child's HIV status and history of antibiotic use. All information will be handled with confidentiality and will only be used for the purpose of the study.

**Risks:** There will be no risks involved in this study.

**Benefits:** There will be no direct benefits to you but the findings will be useful in improving the quality of antibiotic prescribing among children less than 5 years.

Assurance **of confidentiality:** All information obtained from you will be **kept** in confidence. At no point will you or child's name be mentioned or used during data handling or in any resulting publications. Codes will be used instead.

Contacts: In case you need to contact me, my academic department or the Kcnyatta National Hospital/ University of Nairobi Ethics and Research Committee concerning this study please feel free to use the contacts provided above.

I now request you to sign the consent form attached. -

CONSENT FORM

**A COMPARATIVE STUDY OF ANTIMICROBIAL USE IN HIV INFECTED/EXPOSED AND NON INFECTED CHILDREN AT NAIVASHA DISTRICT HOSPITAL, KENYA**

I, \_\_\_\_\_ give consent to the investigators to use my child's file to obtain information for her study. The nature of the study has been explained to me by Dr. Nguri Josephine.

\_\_\_\_\_  
Signature Date

I confirm that I have explained the nature and effect of the study.

\_\_\_\_\_  
Signature Date