Use of Cotrimoxazole Prophylactic Treatment in HIV exposed children and its impact on malaria

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By

Nyanyiwe Masingi Mbeye

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Dedication

To my loving and supportive husband Gilder J. Mbeye for always being there for me. The words of encouragement every morning gave me strength never to give up!

To our sons Shikunzi, Muwemi and Gilder Jr. for enduring Mummy's absence for so long!

To my late father and dearest brother, had you both lived to witness the fruits of your counselling, this would have made you proud

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Nyanyiwe Masingi Mbeye

Introduction and methods

The rapidly growing population of HIV exposed children entails widespread use of cotrimoxazole prophylactic treatment (CPT) to protect them from HIV opportunistic infections given their increased susceptibility compared to non-HIV exposed children. A number of studies have reported that CPT also provides protection against malaria but estimates of its effectiveness vary and there is little information on the impact of the prevalence of antifolate resistance mutations on its effect. Since daily CPT provides prophylaxis against malaria, it could modulate the development of malaria-specific immunity and increase the incidence of malaria after it is stopped (a rebound effect). Moreover, factors that influence CPT adherence in this group are not known. This thesis reviewed studies that examined the effect of CPT provided at the age of 6 weeks to 14 months on malaria incidence in children in Sub-Saharan Africa (**systematic review**) and investigated the incidence of malaria and other morbidities during and after CPT in the first two years of life in HIV exposed children in southern Malawi (**cohort study**). Lastly, CPT adherence was explored using narrative and grounded theory approaches (**qualitative study**).

Results

The **systematic review** included 3 Randomised Controlled Trials (RCTs) and four cohort studies fulfilling the eligibility criteria, with a total of 5,978 children (1,692 HIV exposed; 2,800 non-HIV exposed; 1,486 HIV-infected). Children on CPT were less likely to develop clinical malaria episodes than those without prophylaxis (combined Incidence Rate Ratio (IRR) = 0·37, 95% CI 0·21, 0·66) but there was substantial between-study heterogeneity (I-squared=94%, p<0·001). The protective efficacy of CPT was highest in an RCT from Mali, where the prevalence of antifolate resistant plasmodia was low. In meta-regression analyses there was some evidence that the efficacy of CPT declined with increasing levels of resistance. Mortality was reduced with CPT in an RCT from Zambia, but not in a cohort study from Côte d'Ivoire. In the **cohort study** of 500 HIV exposed and 500 non-HIV exposed children matched on age and residence; the incidence of uncomplicated malaria was 65% lower in year 1 in the HIV exposed group (IRR = 0.35, 95% CI 0.25, 0.49, p<0.001). In year 2 after CPT was stopped, the incidence was similar to that in non-HIV exposed group (IRR = 0.94, 95% CI 0.53, 1.68, p=0.839) among the first 315 children that had completed the follow-up period at the time of the analysis. The same pattern was observed for all-cause morbidity and hospital admissions where a lower risk was observed during year 1 and similar estimates between the groups were obtained in year 2. In the **qualitative study**, Participation in the cohort study empowered HIV infected women to make decisions about their children's health and develop useful strategies to promote uptake of CPT. The women themselves, their families, the communities in which they lived and the health care system related and influenced each other through social interaction which played a role in influencing actions either positively or negatively. Despite negative influences that might have arisen at any level, the determination of the individual to take a health related action and the realisation that the recommended action would prevent any negative outcomes motivated the mothers to believe that they could successfully do something to prevent any negative health outcomes on their children.

Conclusions

CPT significantly reduced the incidence of malaria in children in the systematic review and meta-analysis as well as in HIV exposed children in the cohort study in year 1. Marked reductions in the incidence of severe malaria, all-cause morbidity and hospital admissions during the period in which it was given were observed in the cohort study. Although the cohort study was not able to show any benefits on all-cause mortality, CPT was associated with significant reductions in mortality in the systematic review. The follow up in year 2 is on going but preliminary results suggest that the incidence of malaria does not increase after cessation of CPT at 14 months of age. The improved health outcomes of HIV infected women motivate the women to continue administering CPT to their children despite any deterring factors that might arise.

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Last but not least, I am always thankful to the omnipresent God Almighty for keeping my family and I in good health throughout this time and giving me strength to hold on.

Declaration

This thesis is the result of my work. Three studies: a systematic review and meta-analysis, a cohort study and a qualitative study make up this thesis. For the cohort study, the thesis presents findings basing on 60% of the study follow up time as the study is still on going until end of August 2014. My contribution to all the studies presented in this thesis is as follows:

Activity	Responsibility
Systematic Review and Meta-analysis	
Proposal development	Sole
Search	Shared
Data extraction	Shared
Data analysis	Sole
Prospective Cohort Study	
Day to day management of the study	Sole
Proposal development	Sole
Development of Standard Operating Procedures	Sole
Development of Case Report Forms (CRFs)	Sole
Electronic CRF Programming	Assisted
Study participant recruitment	Shared
Clinic and field follow-ups	Shared
Blood specimen collection	Shared
Medical examination of study participants	Shared
Blood specimen processing	Shared
Data cleaning	Shared
Statistical programming	Shared
Data analysis	Sole
Social Science study	
Development of interview guides	Sole
Data collection	Shared
Data transcription	Shared
Data analysis	Sole
Writing up of thesis	Sole

Nyanyiwe Masingi Mbeye

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Abbreviations & Acronyms

AIC	Akaike Information Criterion
AIDS	Acquired Immunodeficiency Syndrome
ACT	Artemisinin Combination Therapy
AL	Artemether lumefantrine
API	Annual Parasite Rate
ARDS	Acute Respiratory Distress Syndrome
ART	Antiretroviral Therapy
AS	Artesunate
AZT	Zidovudine
BIC	Bayesian Information Criterion
CAB	Community Advisory Board
CBT	Cognitive Behavioral Theory
CHAM	Christian Health Association of Malawi
COMREC	College of Medicine Research and Ethics Committee
CPT	Cotrimoxazole Prophylactic Treatment
DBS	Dry blood Sample
DC	District Commissioner
DVS	Dominant Vector Status
eCRF	Electronic Case report Forms
EID	Early Infant Diagnosis
EIR	Entomological Inoculation Rate
EFV	Efavirenz
EM	Environmental Management
EPI	Expanded programme on Immunisation
FGD	Focus Group Discussion
GCP	Good Clinical Practice
GDP	Gross Domestic Product
GVH	Group Village Headman

HAPA	Health Action Process Approach
Hb	Haemoglobin
HBM	Health Belief Model
HIV	Human Immunodeficiency virus
HIV RNA	Human Immunodeficiency virus Ribonucleic Acid
HMIS	Health Management Information System
HSA	Health Surveillance Assistants
IDI	In depth Interviews
IMCI	Integrated Management of Childhood Illnesses
IPT	Intermittent Preventive Treatment
IPTc	Intermittent Preventive Treatment in children
IPTi	Intermittent Preventive Treatment in infants
IPTp	Intermittent Preventive Treatment in pregnancy
ITN	Insecticide Treated Nets
IRS	Indoor Residual Spraying
LLIN	Long Lasting Insecticide Nets
MDA	Mass Drug Administration
MIS	Malaria Indicator Survey
MMV	Medicine for Malaria venture
MoH	Ministry of Health
mRDT	Malaria Rapid Diagnostic Tests
MUAC	Mid Upper Arm Circumference
NMCP	National Malaria Control Programme
NVP	Nevirapine
OI	Opportunistic infections
PCP	Pneumocystis Carinni Pneumonia
PCR	Polymerase Chain Reaction
PDA	Personal Digital Assistant

PE	Primary Education
P-D	Pyrimethamine-Dapsone
PR	Parasite Rate
PMTCT	Prevention of Mother to Child Transmission
PRISMA	Preferred Reporting Items for Systematic Reviews
QDA	Qualitative Data Analysis
QECH	Queen Elizabeth Central Hospital
RBC	Red blood Cells
RCT	Randomised Clinical Trial
SE	Secondary Education
SCT	Social Cognitive Theory
SMA	Severe Malarial Anaemia
SMC	Seasonal Malaria Chemoprevention
SOPs	Standard Operating Procedures
SP	Sulfadoxine pyrimethamine
SR	Spleen Rate
SSA	Sub-Saharan Africa
TA	Traditional Authority
TDF	Tenofovir
TTM	Trans-theoretical Model
3TC	Lamivudine
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
WHO	World Health Organisation
WWMRN	World-Wide antimalarial Resistance Network
ZCH	Zomba Central Hospital

CHAPTER 1 : GENERAL INTRODUCTION

"Footprints made in the sands of history are not made by the ones sitting down"
- Bob Moawad (modified)

1.1 Introduction

The co-existence of HIV and malaria in sub-Saharan Africa poses serious public health challenges as they both affect children under the age of five and pregnant women more (Steketee, 2001). To date, there has been wide scale up of Prevention of Mother to Child Transmission (PMTCT) of human immunodeficiency virus (HIV) interventions in most settings in sub-Saharan Africa (UNAIDS, 2013c). Sustained progress of the uptake of PMTCT interventions has reduced the incidence of HIV infections in children (UNAIDS, 2013c). Although not infected with HIV, the exposure to HIV in children born to HIV infected women increases their susceptibility to opportunistic infections due to their continued exposure to HIV during breastfeeding and a compromised maternal immune system caused by HIV in the mother, which may lead to reduced transplacental transfer of antibodies to the foetus in utero (Moraes-pinto, 1996). At birth, these children are challenged with increasing numbers of virulent congenital or maternally acquired neonatal infections resulting from increased shedding and higher pathogen levels related to immunosuppression in HIV infected mothers (Moraes-pinto, 1996). This likely interferes with the ability to adequately support development of infant's immune capacity and viral exposure of the foetus in utero resulting in reduced capacity of the infant himself to fight common infections (Chougnet, 2000b, Clerici, 2000). These immunological deficiencies also interfere with the levels of immunoglobulin present in breast milk which are important in protecting infants against infections (Thomas, 2004). In the absence of any form of treatment, HIV infected children have a 2 year median survival (Dunn, 2003) with significantly higher mortality at all ages than their HIV exposed but not infected counterparts (Brahmbhatt, 2006) although when compared with non-HIV exposed children, HIV exposed children, have a 16% higher mortality (Brahmbhatt, 2006). Severe morbidity and early mortality in HIV infected and HIV exposed children more than doubles when maternal CD4 counts are low and HIV viral load (HIV RNA) is high (Brahmbhatt, 2006). Without any mitigating interventions these children experience high fatality rates of between 40-90% from PCP, a severe form and rapidly progressive pneumonia that generally occurs between 3 and 6 months of life, often as the first sign of HIV infection and before child is definitively determined to be HIV infected (Rabkin, 2005).

As a preventive measure, HIV exposed children are currently being given daily cotrimoxazole prophylactic Treatment (CPT) from the age of four to six weeks or at their first encounter with the formal health services, until they stop breastfeeding and are no longer at risk of getting infected (WHO, 2009b). Cotrimoxazole has been shown to be effective in reducing bacterial infections even in areas where there is a high background *in vitro* resistance to it (Chintu, 2004). In addition, it potentially offers an effective and sustained malaria chemoprophylaxis, even in areas like Malawi, Uganda and others where resistance to sulphonamides may be high (van Oosterhout et al., 2005), and significantly lowers incidence of malaria episodes, both parasitaemic and presumptive among both HIV exposed and HIV infected children (Graham, 2010). This could potentially impair the acquisition of natural immunity to malaria in infants and therefore abrupt cessation of cotrimoxazole use at 12 months after stopping breastfeeding in children who remain HIV-negative could be associated with an increased risk of malaria in terms of frequency and severity in the following year. There is a wide variation between studies on the effect of CPT on malaria hence the studies described in this thesis are designed to systematically review the effect of CPT on malaria incidence and investigate the risk and benefits associated with its use in HIV exposed infants during the period that they are taking it and in the year after they have stopped but also understand the household level impact related to administering daily CPT to HIV exposed children.

Presently in Malawi, there is an 'opt out' system where all pregnant women are encouraged to test for HIV (Health, 2012). Therefore, all women are offered HIV testing and those found positive are offered anti-retroviral therapy (ART) which is usually a combination of Tenofovir (TDF), Lamivudine (3TC) and Efavirenz (EFV). This is a modification of the newly WHO recommended PMTCT regimen also known as Option B+ for all HIV infected as well as breastfeeding women. Breastfeeding infants born from these mothers are given Zidovudine (AZT) or Nevirapine (NVP) from birth until 4-6 weeks (Health, 2012). Between the age of 4-6 weeks, guardians bring infants to the PMTCT clinic where a filter paper sample is taken for HIV PCR testing. If positive they start on ART immediately. However if the infant is negative and the mother would like to breastfeed, infants are put on daily CPT for the entire period they are breastfeeding. They are then requested to return to the PMTCT clinic every month for review. Using the present WHO guidelines on HIV and infant feeding (WHO, 2009a), mothers are recommended to breastfeed until the child is 12 months old and/or even more. Studies in

Malawi have generally reported low uptake of PMTCT interventions largely related to fear of negative community reactions, lack of spousal support and also failure to disclose one's HIV status (Chinkonde, 2009, O'Gorman, 2010)

1.2 Study Aims and Objectives

1.2.1 Overall Objective:

To investigate the risks and benefits of daily CPT in HIV exposed children on malaria and other co-morbidities, and explore the perceptions around the impact at household level of administering daily CPT.

1.2.2 Specific Objectives:

- To systematically review the effect of CPT on the prevention of clinical malaria and all-cause mortality in HIV positive and HIV exposed children in different settings in sub-Saharan Africa by conducting a systematic review of the literature and a meta-analysis.
- To compare the incidence of uncomplicated and severe malaria, all-cause sick visits, all-cause hospital admissions and all-cause mortality in HIV exposed children before and after stopping daily CPT to non-HIV exposed children in a cohort study in southern Malawi.
- To explore the lived experiences of HIV positive mothers giving daily CPT to their children by conducting a social science study in southern Malawi.

1.3 Thesis Structure

This thesis is presented in six chapters. Chapter one presents the introduction/background information to the study area and introduces the overall aim and specific objectives for the thesis. Chapter two gives a detailed review of the literature highlighting relevant evidence on the subject matter. The systematic review and meta-analysis follow in chapter three presenting available evidence on the use of cotrimoxazole for preventing malaria in sub-Saharan African children. Chapter four provides the introduction, methods, results and discussion for a large epidemiological cohort study comparing the effect of CPT in the period when HIV exposed children were taking daily CPT (year 1) and the period when they had stopped (year 2). The qualitative study on experiences of HIV infected mothers

administering daily CPT to their HIV exposed but uninfected children are presented in Chapter five.

Most chapters are separate studies on their own and addressing a specific objective given in the introductory chapter of the main thesis. For example, chapter three addresses specific objective number one while chapter four and five address specific objectives two and three respectively. At the end in chapter six, a general discussion, recommendations and conclusions for all the three studies are presented. Figure 1.1 illustrates the structure of this thesis.

1.4 Definition of Terms

HIV Exposed children: Infants or children born to mothers living with HIV

Non-HIV Exposed children: Infants or children born to mothers not living with HIV (HIV negative mothers)

HIV Infected children: Infants or children infected with HIV

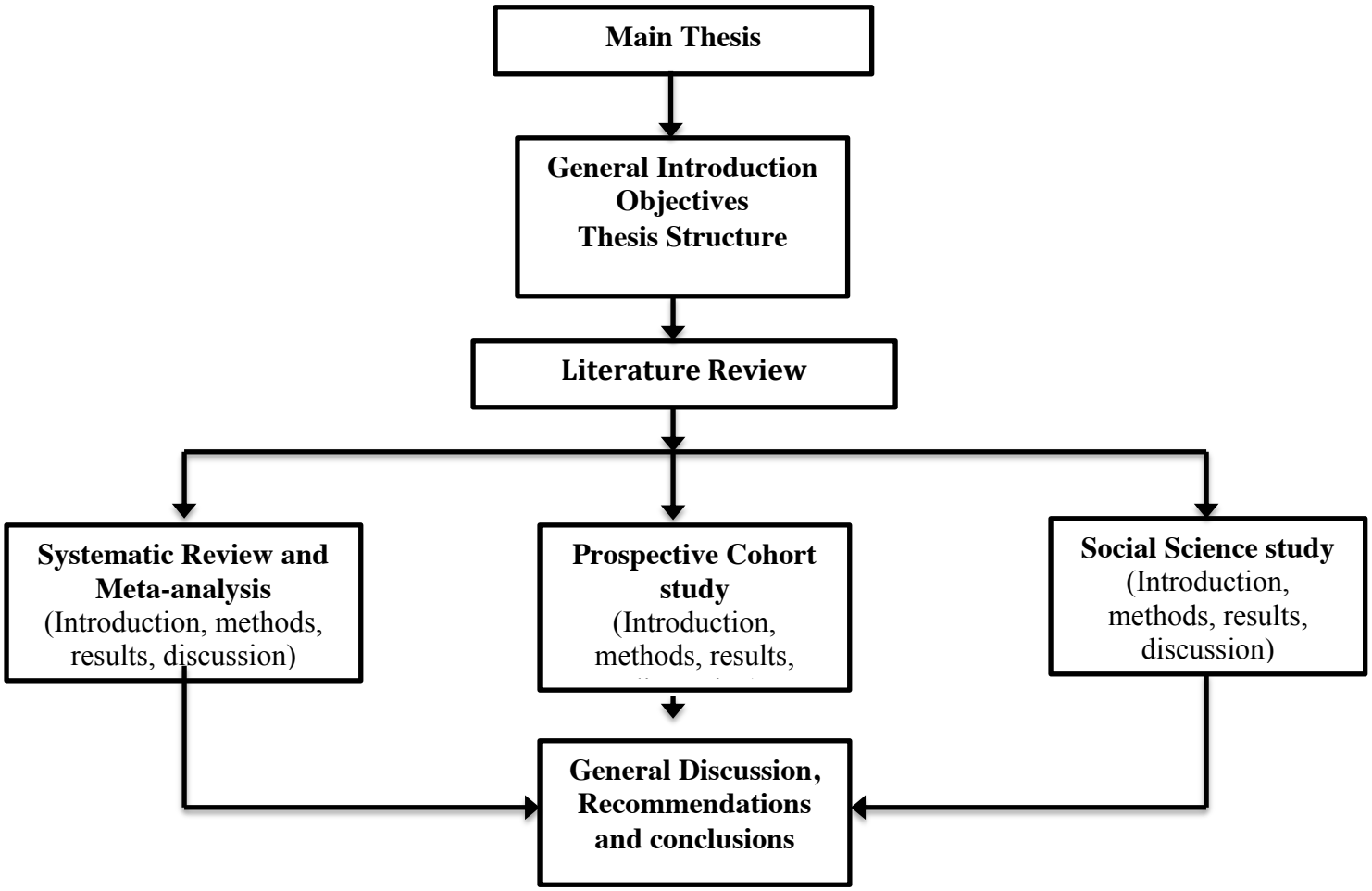
Adherence to medication: The extent to which patients take medications as prescribed by their health care providers

Rebound malaria: A hypothetical overshoot that could occur in populations that have lost their immunity

Uncomplicated malaria: Symptomatic infection with malaria parasitaemia without signs of severity and/or evidence of vital organ dysfunction

Severe Malaria: Acute malaria with major signs of organ dysfunction and/or high level of parasitaemia

Figure 1.1: An illustration of thesis structure



CHAPTER 2 : LITERATURE REVIEW

2.1 Introduction

This chapter describes an up to date understanding of the epidemiology of malaria in children in the context of this study, available malaria control interventions and factors influencing uptake and impact of these interventions on households.

2.2 The Malaria Parasite

Severe malaria and deaths in endemic Africa are mostly attributable to malaria resulting from infection with *Plasmodium falciparum* parasites, which is the most virulent of the five species of *Plasmodium* known to infect man *(P. falciparun*, *P. vivax*, *P. malariae*, *P. ovale and P. knowlesi)*. Briefly, *P. falciparum* is more prevalent in Africa south of the Sahara (Mmbando et al., 2009). Its characteristic feature of destroying red blood cells and adherence to cells in certain tissues gives rise to problems such as severe malarial anaemia and cerebral malaria respectively resulting in death (Mmbando et al., 2009). *P. vivax* is another important malaria species that is recognized to have a more widespread distribution primarily occurring in areas outside Africa. Its ability to survive in cooler climates allows it to develop inside the mosquito vector at lower temperatures subsequently causing infections during winter periods when *P. falciparum* is less prevalent (WHO, 2013b). The most minor of the Plasmodium species are *P. ovale* and *P. malariae* whose infections are mild in nature and less prevalent in most endemic areas. The unusual characteristic feature of *P. malariae* is its chronic blood stage infection which may take years (Institute, 2013). Recently, *P. knowlesi,* a simian malaria parasite with similar clinicopathological syndrome to *P. falciparum* has been established as a fifth human *Plasmodium* species. This parasite is commonly found in forest areas of Southeast Asia in Malaysia, Singapore and other countries in the region initially affecting humans in close proximity with macaque monkeys but recent data indicates that *P. knowlesi* might exist in communities further from the forests (Drakeley, 2014). This knowledge has led to more studies being currently conducted by a consortium led by the London School of Hygiene and Tropical Medicine. The aim is to characterise the biological, environmental and social factors responsible for causing infections within human populations and determine the magnitude of public health threat caused by *P. knowlesi* (Drakeley, 2014). Its unique feature that distinguishes it from *P. falciparum* is that it does not sequester significantly in the microcirculation (White, 2008). Previously, *P. knowlesi* was misdiagnosed as *P. malariae*

because microscopy could not differentiate the two. However, following results from nested Polymerase Chain Reaction (PCR) speciation assays, Singh *et al* were able to confirm that *P. knowlesi* was responsible for causing malaria in humans (White, 2008, Singh, 2008).

In most malaria endemic areas, infections caused by two or even more malaria parasites are more frequent. In tropical regions, *P. falciparum* and *P. malariae* tend to occur together while mixed infections of *P. falciparum* and *P. vivax* are common in sub-tropical areas. When this happens, the complications of *P. falciparum* which usually tend to be the dominant species are reduced (Warrell, 2002). Since parasite detection mainly targets *P. falciparum* in most settings where *P. falciparum* is dominant, *P. vivax* may be missed during diagnosis resulting in its reappearance after some time. This requires appropriate programming of control interventions. There have also been mixed infections of *P. falciparum* and *P. ovale* (Warrell, 2002).

2.3 The malaria burden in children in sub Saharan Africa (SSA)

The survival of children early in life is adversely affected by exposure to malaria during pregnancy which in addition to contributing to spontaneous abortions and stillbirths, largely accounts for premature delivery, low birth weight and overall mortality (Murphy, 2001, Desai, 2007). Murphy and Breman estimated that each year, each child aged <5 years experiences four to nine febrile episodes of which 30-60% is a result of malaria (Murphy, 2001). These febrile illnesses are a major cause of hospital admissions in SSA (Murphy S.C., 2001). An analysis of 200 articles on malaria in children, showed that the annual hospital admission rate for children <5 years presenting with malaria or malarial febrile episodes is 31/1000 which translates to almost 3 million children with malaria who are admitted to clinics each year in endemic areas (Murphy S.C., 2001). Moreover, as much as 20% of all deaths in children under five years of age in Africa are attributable to malaria (WHO, 2001). WHO estimates show that in 2012, 80% of the more than 200 million *P. falciparum* malaria episodes worldwide and 90% of all deaths from malaria occurred in Africa (WHO, 2013b). Of these malaria deaths, 77% were among children under the age of five (WHO, 2013b). Apart from preterm delivery and low birth weight; complications of severe malaria such as cerebral malaria and severe malarial anaemia (SMA) are principle ways in which malaria contributes

to child mortality (Murphy S.C., 2001). African vectors have a long life span and a strong human-biting behaviour which may suggest why more than 90% of the global malaria deaths are occurring in Africa (WHO, 2003b).

2.4 The health situation and malaria in under-five children in Malawi

2.4.1 Health profile for under-five children in Malawi

According to a United Nations Children's Fund (UNICEF) report, over 600 children are born every year in Malawi. The majority of these (94.5%) are initiated on breastfeeding immediately after birth and 86.4% are introduced on supplementary foods by the age of between six and eight months. The neonatal, infant and under-five mortality rates in Malawi in 2012 were estimated to be 24, 46 and 71 per 1,000 live births (Table 2.1). The under-five mortality rate decreased markedly from 244/1000 live births in 1990 to 71/1,000 live births by 2012. The most common causes of morbidity in the under-fives between 2008 and 2012 in these children were pneumonia (70.3%), followed by diarrhea (69%). During this period, 32.5% of the children who had a febrile illness were treated with an antimalarial (UNICEF, 2013). Although there has been great achievements in the scale up of PMTCT interventions and that these have led to the reduction of new HIV infections among children globally, 180,000 children aged 0-14 years were still living with HIV in Malawi in 2012 (UNAIDS, 2013c).

Table 2.1: Selected basic health indicators for children in Malawi

Indicator	
Total population under-five children (million) in 2012[1]	2.8
Under-five mortality rate (per 1,000 live births) in 2012	71
Infant mortality rate (per 1,000 live births) in 2012	46
Neonatal mortality rate (per 1,000 live births) in 2012	24
Annual number of births (per 1,000 total population), 2012	638.9
Annual number of under-five deaths (thousands), 2012	43
Prevalence of low birth weight (%), 2008-2012	13.5
Early initiation of breastfeeding (%), 2008-2012	94.5
Exclusive breastfeeding <6 months (%), 2008-2012	71.4
Breastfeeding at age 2 years (%) 2008-2012	76.8
Pneumonia (%) 2008-2012, care seeking for suspected pneumonia	70.3
Diarrhoea (%), 2008-2012 treatment with ORS	69
Malaria (%) 2008-2012, antimalarial treatment among febrile children	32.5
Children aged 0-14 years living with HIV 2012	180,000
Orphans due to AIDS 2012	770,000
Women aged 15 and above living with HIV 2012	560,000
HIV prevalence (%) among pregnant women 2012	10.6
Source: http://www.unicef.org/infobycountry/malawi_statistics.html	

2.4.2 Provision of health Services in Malawi

The Ministry of Health (MoH) is the main provider of health services in Malawi providing about 60% of all health services. The Christian Health Association of Malawi (CHAM) is the second largest provider contributing about 37% of health services. The remaining 4% is shared among the Ministry of Local Government, private sector and commercial companies (Health, 1999). These services are provided at three main levels: primary, secondary and tertiary. In Zomba district, free public health services are provided at Zomba Central hospital (ZCH) and 33 Health Centres run by the Zomba District Health Office (MLGRD, 2013). The mission hospital and private hospitals offer their services at a fee. Zomba Central hospital is a tertiary hospital under the MoH serving as a referral hospital for all the other hospitals in the whole eastern part of the southern region. However, because there is no district hospital in the district, it also serves as a district hospital.

[1] Projected under-five population by the National Statistics OfficeNSO. 2008. 2008 Population and Housing census. *National Statistics Office, Zomba, Malawi*.

2.4.3 The malaria disease burden in under-five children in Malawi

Estimates by the Health Management Information System (HMIS) show a rise of approximately 40% in new cases of malaria in the general population from 3.6 million in 2004 to 6.1 million in 2009 despite successful implementation of malaria control interventions outlined in the 2005-2010 national malaria strategic plan (MoH, 2005b). These infections account for more than 33% of all outpatient visits and remain the principle cause of morbidity and mortality in pregnant women and under-five children (MoH, 2012) and a leading cause of hospital admissions in these children (Buhendwa, 2008). Most of the hospitalisations from malaria and anaemia (often attributable to malaria) are also responsible for about 30% of all hospital deaths in under-five children (Buhendwa, 2008). Malawian children under the age of five, just like elsewhere in parts of endemic Africa, are at the greatest risk because during this time they have lost the immunity they acquired transplacentally from their mothers and have not yet acquired adequate protective immunity against severe malarial disease (Ndawala J., 2000). However, severe disease and death from malaria decline as the children grow (Snow, 1998) mainly because of acquisition of malaria specific immunity which is achieved by exposure to malaria infection (Doolan, 2009).

2.4.4 Malaria transmission in Malawi

Malaria occurs throughout the country all year round. Hospital based data by the HMIS indicates that there were 6.1 million malaria cases in 2009 (MoH, 2011b) representing nearly 50% of the whole population. Half of these occurred in children under the age of five. However, these figures could likely increase if community based active malaria surveillance data were also used together with hospital data to estimate prevalence. For instance, a recent nationwide Malaria Indicator Survey (MIS) reported a malaria prevalence rate of 43% in children aged between 6 months and five years who did not show any malaria symptoms (MoH, 2012). The MIS is a nationally representative assessment of the coverage of malaria control strategies conducted every two years within six weeks of the end of the rainy season in malaria endemic countries mostly in sub Saharan Africa (MoH, 2012).

2.4.5 Common malaria vectors in Malawi

In Malawi, malaria is endemic in 95% of the country with over 98% of malaria infections caused by *Plasmodium falciparum* (Buhendwa, 2008, Mzilahowa, 2012). The main malaria vectors prevalent in Malawi are *Anopheles funestus, Anopheles gambiae* and *Anopheles arabiensis (Spiers, 2002, Mzilahowa, 2012).* Some variation from high to low malaria transmission intensity has been observed within Malawi such that areas with higher temperatures along the lakeshore and lowlands of the lower Shire experience high malaria transmission resulting in average annual infection prevalence of more than 40% or more compared to upland areas which have relatively cool temperatures especially in most parts of the Northern region of Malawi with average annual infection prevalence of less than 5% (Gething, 2011, Services, 2007). High transmission has also been observed during the rainy season that begins in October and lasts in April in most parts of the country. Although a decrease in malaria-specific mortality by 2.2% was registered during the period 2004 to 2009, a steady increase in malaria incidence was observed among both under five children and those aged more than 5 years over the same period (MoH, 2010, MoH, 2012).

2.4.6 Strategies for malaria control in Malawi

In its efforts to curb malaria, the government of Malawi through the National Malaria Control Programme (NMCP) has ranked malaria as one of its priorities in the Essential Health Package that aims at directing scarce resources to public health and clinical services provided for free at both primary and secondary care levels (Njie H., 2007). This has been the most effective and efficient way of improving health services delivery in resource limited settings like Malawi. With assistance from its development partners, the government of Malawi embarked on scaling up different malaria control interventions as outlined in its 2011-2015 National Malaria Control Strategic plan (MoH, 2011b) with a goal to achieve universal access of all malaria control interventions by 2015 through:

- Increasing the proportion of those suffering from malaria who have access to and are able to use correct, affordable and appropriate treatment within 24 hours of onset of symptoms from 21.9% to 50%

- Increasing the proportion of pregnant women who have access to and receive two or more doses of Intermittent Preventive Treatment in pregnancy (IPTp) for malaria prevention from 60.3% to 80%
- Increasing percentage of children under five years of age sleep under an Insecticide treated Net (ITN) from 55.4% to 80%
- Increasing percentage of pregnant women sleep under an ITN from 49.4% to 80%
- Increasing number of high burden districts implementing Indoor Residual Spraying (IRS) from 1 to 12
- Increasing number of households owning at least one ITN from 58.1% to 90%
- Increasing percentage of out-patient suspected malaria cases who are confirmed by microscopy to 50%
- Increasing percentage of out-patient suspected malaria cases who are confirmed by malaria Rapid Diagnostic Test (mRDT) from 0% to 80%

2.4.7 Uptake of malaria control interventions in Malawi

One year into implementation of the 2011-2015 malaria strategic plan, progress in uptake of some malaria control measures is being registered as reported by the 2012 Malaria Indicator survey (MIS) report notably the increase from, 55.4% to 56% in the proportion of children under the age of five sleeping under an ITN in the previous night. During the same period, the proportion of children aged below five years with fever who had received an effective antimalarial treatment on the same day or next day increased by over 40% (MoH, 2012). Although vector control measures such as IRS are implemented at a small scale in specific districts, there has been an increase in scale of implementation from 2% of all households in 2010 to 9% of all the households in 2012 (MoH, 2012, MoH, 2010). Despite the gains achieved with malaria control interventions, the disease still remains a serious public health problem and the need for strengthening uptake of these interventions and exploration of complimentary interventions cannot be overemphasized. Table 2.2**Error! Reference source not found.** is a summary of current uptake of malaria control interventions in children aged below five years.

Table 2.2: Malaria status and uptake of some control interventions in under-five children in Malawi in 2012

Age in months	Malaria prevalence by mRDT	Prevalence of anaemia Hb<8g/dl	Proportion with fever treated with an effective antimalarial within 24 hours	Proportion slept under an ITN in the previous night
6-8	35.9	13.0	68.1	62.7
9-11	31.7	16.6		
12-17	31.6	12.9	64.0	58.3
18-23	39.0	11.0		
24-35	46.1	9.4	68.8	55.1
36-47	46.7	7.3	63.3	55.3
48-59	50.0	4.1	57.6	48.9

Source: Adapted from MIS report 2012 (MoH, 2012); Hb: Haemoglobin

2.5 The vectors capable of transmitting malaria from man-to man

The malaria parasite is transmitted from man-to-man exclusively through the bites of female anopheles mosquitoes (WHO, 2003b) which are capable of transmitting the parasite to hundreds of individuals in a space of few months making it more infectious than HIV. There are about 400 different species of *anopheles,* but there are only about 60 that are vectors of malaria and of these, about 40 are important. The most important vectors in SSA are the *An*. *gambiae* complex, *An*. *arabiensis*, *An*. *funestus*, *An*. *melas* and *An*. *merus* (Service, 1996, Sinka E.S., 2010). The salt water tolerant coastal species of the *An*. *gambiae* complex like *An*. *melas* and *An*. *merus* despite not being as efficient at transmitting malaria as *An*. *gambiae* and *An*. *Arabiensis,* they are often found in high densities that they also achieve the Dominant Vector Status (DVS) (Bryan, 1983, Cuamba, 2009).

It has been observed that distribution and abundance of the mosquito vector is determined by temperature and extent of water availability for larval breeding; seasonal fluctuation of mosquito populations; vectorial capacity (the number of new infective bites received daily by a single host) (Eldridge B.F., 2004) of the common vector species and duration of conditions suitable for mosquito survival (Shiff, 2006b). The best combination of adequate rainfall,

temperature and humidity have been associated with creating favourable conditions for breeding and survival of anophelines in the tropical areas of the world (CDC, 2010). All of the important vector species bite at night and they breed in shallow collections of freshwater. More intense transmission is said to occur in places where the mosquito is relatively long-lived (so that the parasite has time to complete its development inside the mosquito) and where it prefers to bite humans rather than animals (WHO, 2003b). This information suggests that understanding of malaria epidemiology is key to planning and targeting of effective control interventions.

2.6 Malaria endemicity and disease pattern

Several ways are used to measure the intensity of malaria transmission. The most direct measurement is the use of Entomological Inoculation Rate (EIR) which refers to the number of infectious bites per person per unit time usually measured or expressed per year. This method has been used to quantify the parasite-infected mosquito pool and its tendency to transmit parasites to human population (Shaukat A.M., 2010). In order to measure the prevalence of peripheral blood-stage infections in the community, the parasite 'rate' (PR) (the proportion of the population or sample that is infected with asexual stage parasites) (Hay, 2008, Gething, 2011) has been utilised. In younger children aged between zero and eleven months in areas with perennial intense transmission, the parasite rate constantly exceeds 75% (MAP, 2010). This happens because of increased susceptibility to malaria due to lack of malaria specific immunity in this age group. Moreover, similar estimates have been observed with the use of spleen rates to describe endemicity patterns of malaria in different regions (Warrell, 2002). These two measurements however, fall short of capturing the seasonality in transmission of malaria as compared to EIR. The strengths and weaknesses of these measurements as summarized in Table 2.3 may guide in the selection of a more appropriate method depending on the context.

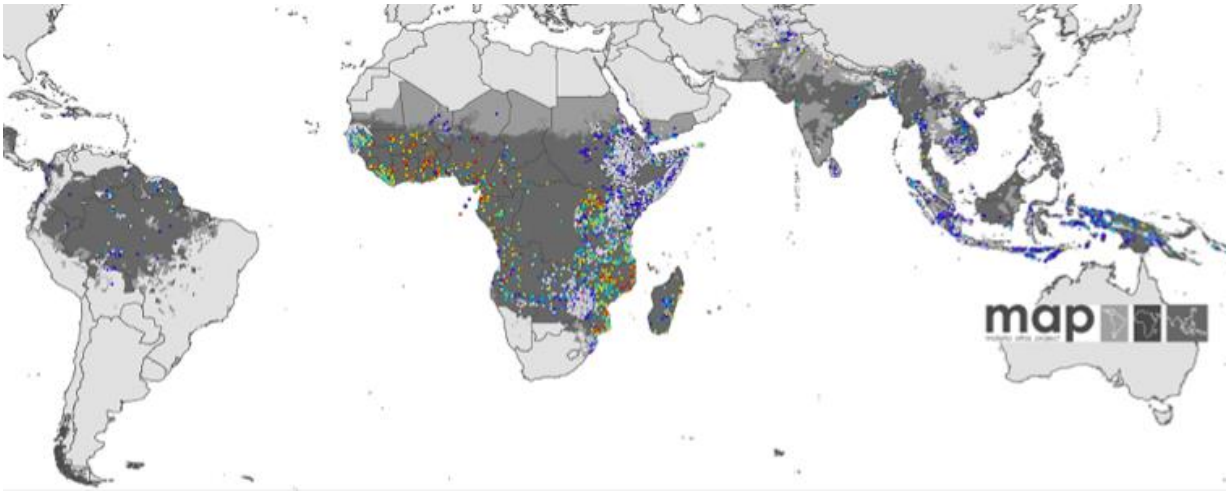
Table 2.3: Indices of malaria transmission

Index	What is measured	Advantages	Disadvantages
Entomological Inoculation Rate (EIR)	Infectious bites per unit time (usually per year)	Direct reflection of vector control and antigametocidal drugs	• No standard protocols • Variability in methodologies • Few trained specialists
Parasite Rate (PR)	Proportion of the population found to carry asexual parasites in RBCs; can also assess gametocyte rates; by age group	Direct reflection of inoculation, immunity and treatment effectiveness in humans	• Microscopy 'gold standard' • Prone to technical efforts • Changes may occur following environmental and control factors
Annual Parasite Index (API)	Number of parasite infections in a well-defined geographical area; usually per 1,000 persons per year	Direct reflection of all prevention and control effects on humans	• Depends on active case detection system, which is often poor
Spleen rate (SR)	Proportion of children 2-9 years of age with a palpable spleen	Non-invasive, indirect way of measuring impact of malaria on spleen	• Variability in examiners; • Many causes of splenomegaly; • Point prevalence measurements can vary/change rapidly

Source: Shaukat, A.M., et al., Malaria journal, 2010; 9:122 (Shaukat A.M., 2010); RBC: Red Blood Cells

Malaria transmission tends to vary across regions. On one end of the transmission spectrum is stable transmission which is characterised by intense transmission either throughout the year or during the rainy season. On the other end is unstable transmission with seasonal transmission under normal rainfall conditions and a decline in transmission in times of drought. However, *P*. *falciparum* malaria transmission is endemic in most parts of Africa, Southeast Asia and South America (Figure 2.1) (Gething, 2011).

Figure 2.1:The spatial distribution of Plasmodium falciparum malaria endemicity in 2010



Source: Gething et al, Malaria Journal 2011. http://www.malariajournal.com/content/10/1/378
Key: Dark grey areas = Stable malaria (PfAPI ≥0.1 per 1,000 pa; Medium grey areas = Unstable malaria (PfAPI<0.1 per 1,000 pa); Light grey areas = No risk (PfAPI = 0 per 1,000 pa) (Gething, 2011)

This geographical variability in malaria transmission intensity, explains why population groups at risk of malaria also differ as well as their control measures. It is estimated that the majority of deaths in tropical Africa occur in areas of stable transmission of *falciparum* malaria. In these areas, the two groups at highest risk are very young children, mainly because they have not yet acquired clinical immunity and pregnant women, whose immunity to malaria is temporarily impaired (WHO, 2003b, Chuma J., 2010). Evidence of more adult malaria has been observed in areas of unstable transmission often with low transmission intensity especially during the rainy season. Unlike in stable malaria transmission areas, in unstable areas, children aged between 4 and 6 easily succumb to cerebral malaria. Nevertheless, seasonal morbidity is seen in all population groups (Shiff, 2006b).

2.7 Determinants of malaria transmission

Historically, malaria transmission has been associated with both climatic and non-climatic factors in addition to social and human host factors.

2.7.1 Climatic factors

Climate refers to "the average pattern of variation in temperature, humidity, atmospheric pressure, wind, precipitation, atmospheric particle count and other meteorological variables in a given region over long periods of time" (NASA, 2005, NAMC, 2014, Skybrary, 2014). At global level, climatic factors significantly influence the pattern and level of malaria transmission. Among the factors outlined in the definition; temperature, rainfall and humidity have been described to directly influence malaria transmission.

2.7.1.1 Temperature

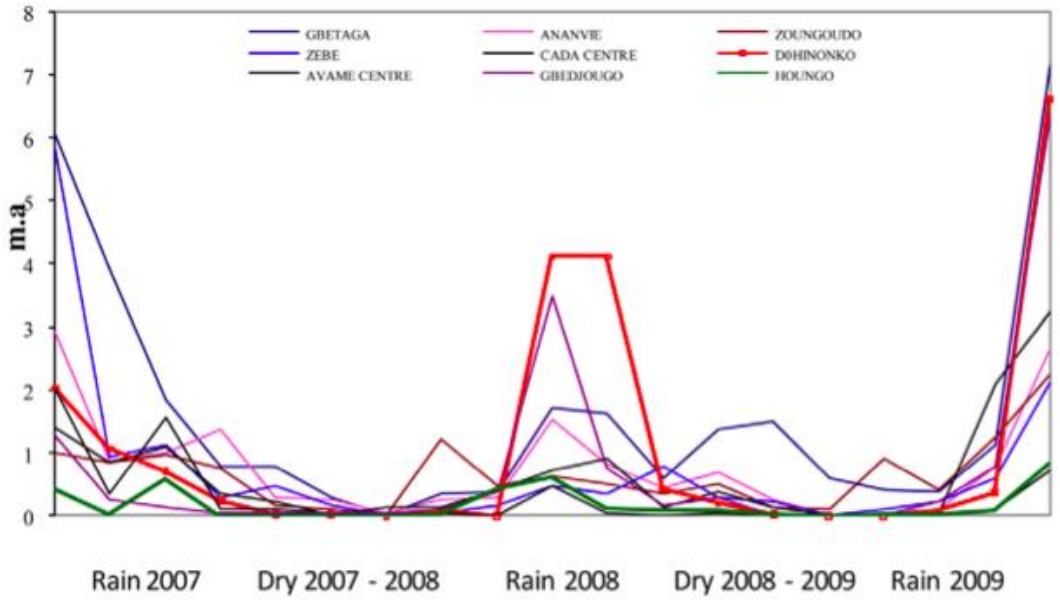
Temperature highly influences development of both the vector and parasite. Increases of about 30-100% in mosquito abundance have been associated with an increase of just 0.5 degrees Celsius in temperature and more recent modelling suggests that even at relatively lower temperatures such as 26 degrees Celsius, malaria transmission can occur (Mordecai, 2013) compared to previously reported temperature ranges of 32-33 degrees Celsius for endemic transmission and optimum rate of spread in disease-free regions (Craig, 1999, parham, 2010). Optimal temperatures are believed to increase the number of blood meals and reproduction resulting in the abundance of mosquitoes (Clements, 1992) and allow for successful development of the parasite to reach the infective stage within the mosquito furthermore facilitating the process of sporogony. In contrast, very low temperatures have been shown to delay this process while higher temperatures on one hand are associated with more rapid development of vectors and increased frequency of feeding by female anopheles mosquitoes. However, when the temperatures are very high, they lead to the development of smaller and less fertile adult mosquitoes. High levels of malaria transmission have been reported to occur in low-lying areas and most tropical areas because these areas have favourable conditions for malaria transmission like warmth and constant temperatures than highlands (Atieli, 2011, Minakawa, 2006).

2.7.1.2 Rainfall

Another important determinant of malaria transmission is rainfall. This explains high malaria transmission after the rainy season in most areas of unstable transmission (Shiff, 2006a). In the Africa Sahel where malaria is predominantly seasonal, malaria incidence increases by more than 2-fold during the rainy season compared to the dry season affecting younger

children aged 2-4 years more than older children. This is largely attributed to the high EIR of 0.78 infective bites/person/per night resulting from fluctuation of mosquito abundance as *Anopheles gambiae* s/l. are seen to breed more prolifically in temporary and turbid water bodies such as ones formed by the rains (le sueur, 1988). Very excessive rains however, have been associated with washing away of slowly moving waters where mosquito larvae breed resulting in disruption of breeding sites as mosquito larvae and pupae get stranded along the banks of streams and some are washed away (Warrell, 2002) although in some highland areas in Uganda excessive rainfall has been associated with increased malaria (Kilian, 1999). A study in western Kenya observed that with a monthly 10 millilitre increase in rainfall, malaria cases increased from 1.4% to 10.7% in the highlands with a 2-3 month lag time (Hashizume, 2009). However, the situation might be different in low-lying areas. **Figure 2.2** demonstrates the association between rainfall and vector density. High vector density was observed during the rainy season compared to the dry season when a series of entomological surveys based on human landing catches in Benin (Cottrell, 2012) were conducted. In these surveys, mosquitoes were collected between 10 pm and 6 am every six weeks for two years and rainfall was recorded twice daily. High parasite density was present during the rainy season compared to the dry season. This demonstrates the significant contribution of rainfall on malaria transmission, as highland areas are usually associated with low transmission.

Figure 2.2: Number of Anopheles gambiae s.l. collected per man per day as a function of rain



Source: Cottrel, G., Kouwaye, B., et al., PloS One 7(1); 2012 (Cottrell, 2012)

2.7.1.3 Humidity

There is lack of studies that have demonstrated the direct relationship of humidity on its own to malaria transmission. The distribution of the mosquito vector has mainly been related to relative humidity which refers to the amount of moisture in the air at a specific temperature, expressed as a percentage (Yang, 2010). Temperature thus plays a major role in determining the extent of malaria transmission (Yang, 2010). Areas with relative humidity of more than 60%, have been associated with the increase in the longevity of adult vectors (Warrell, 2002) which even doubles when relative humidity reaches 80% (Ye, 2008). With high relative humidity, mosquitoes have shown to have better survival and their activity increases. This may explain why they prefer to feed during the night as the relative humidity is higher at night (Haque, 2010).

2.7.2 Non-climatic factors

2.7.2.1 Malaria vectors

The variability in the transmission ability of different species of mosquitoes depends on the biology and behaviour of the mosquitoes themselves. The *Anopheles gambiae* group are

known as the most efficient malaria vectors in the world (Sinka, 2010). Their preference to bite human beings than feeding on animals and their ability to occupy and breed in a wide range of sites (Takken, 2003) partly explains the higher malaria incidence in Africa where the *An*. *gambiae* is predominant compared to the other parts of the world.

2.7.2.2 Social Factors

The local and regional differences in levels of socio economic development may explain the variability in malaria burden (Breman et al., 2004). Factors observed to determine this variability include access to health care and health education, quality of housing, general poverty as well as the existence of active malaria control programmes that provide access to malaria prevention and treatment measures (WHO, 2005b). This explains high burden of malaria in poorest nations in Figure 2.1 (CDC, 2010, Gething, 2011) where poverty is often wide spread and access to health services is often poor (Wang, 2005). These countries generally have the least resources for adequate control efforts (WHO, 2003b) while in developed countries, industrialization and improved housing conditions were instrumental in the elimination of malaria (Budiansky, 2002). The process of urbanization in these areas eliminated open spaces for mosquito breeding, increased pollution of the remaining breeding sites thereby limiting the dispersion opportunities for adult mosquitoes (Lindsay, 1990) and lowering of the vector densities resulting in decreased malaria exposure per capita (Trape, 1987, Smith, 2004). Although most African settings are currently undergoing urbanization, the process is often marked with poor drainage systems, sanitation and housing and wide economic imbalance that have facilitated malaria transmission (Wang, 2005). The problem of urban malaria has been recognized by many authors and following this, a meeting convened by the Knowledge Program at the Liverpool School of Tropical Medicine and the International Water Management Initiative/System-wide initiative on malaria, issued the Pretoria Statement on Urban Malaria that emphasized the need to protect vulnerable people from effects of urban malaria in order to preserve their livelihoods and build conditions for economic growth and to avoid diversion of scarce resources away from rural areas (Donnelley, 2005). Unless appropriately addressed, urban malaria in SSA will remain a major public health problem.

2.7.2.3 Human host factors

Host susceptibility to malaria plays a major role in malaria disease pattern. Epidemiologic studies conducted in areas of high malaria transmission in Africa and Southeast Asia; indicate an age-dependent development of protective immunity against malaria (Sharma K.S., 2004). The acquisition of clinical immunity to malaria is said to be dependent upon the frequency of parasite exposure from birth (Doolan, 2009). Consequently, the age at which disease presentation heightens, the clinical span of disease and the life-time risks of disease, appear to be influenced by the intensity of transmission in a given community (Snow, 1998). As a result of this, malaria mortality is highest during the first few years of life in areas with high transmission rates. However in the absence of any sustained malaria prevention strategies, by the age of five, most children develop a considerable degree of immunity which reduces the risk of *P*. *falciparum* malaria specific mortality, provides protection against severe disease and reduces the frequency of clinical malaria episodes (Sharma K.S., 2004) (Marsh, 1992). For this reason, young children in Africa are more likely to die from malaria as they are yet to develop their immunity, whereas in areas with less transmission and low immunity, all age groups are at risk (WHO, 2000b). In HIV infected and HIV exposed children, the process of acquiring malaria specific immunity in the presence of an inadequate transplacental transfer of immunoglobulins from the HIV infected mother (Moraes-pinto, 1998) and effective malaria prevention strategies (Chougnet, 2000a) is complex.

2.8 Malaria Diagnosis

Several methods for diagnosing malaria are in use in many parts of the world. Malaria can be diagnosed by using laboratory methods as well as clinical methods (Wilson, 2013). Table 2.4 summarizes the most commonly used methods, their advantages and disadvantages. For laboratory diagnosis, WHO recommends use of both microscopy and malaria Rapid Diagnostic Tests (mRDTs) for detection of malaria parasites in places where both are available (WHO, 2011). In such circumstances, microscopy helps in confirming whether mRDTs are able to detect malaria when determination of parasite density is required. In terms of clinical diagnosis, medical personnel can diagnose the disease using the medical knowledge and other signs and symptoms presented by the patient. However, self-diagnosis is also a common method in many African settings where patients diagnose themselves as

having malaria. For example, in Sierra Leone, more than 75% of individuals reported to have diagnosed themselves after experiencing symptoms suggestive of malaria (Ansumana, 2013).

Table 2.4: Description of available malaria diagnostic methods

Method	Sensitivity/Specificity	Advantages	Disadvantages
Rapid diagnostic test: based on pLDH: (Optimal-Flow Inc)	Sens: 93.2% Spec: 98.5%	□ Differentiates *P.falciparum* from non-falciparum infections □ Speed and ease of use; minimal training requirements to achieve reliable result □ Reportedly does not remain positive after clearance of parasites □ No electricity, no special equipment needed; could be used in community outreach programmes	□ Cannot differentiate between non-falciparum species □ Will not quantify parasitaemia
Rapid diagnostic stick test based on PfHRP-II: (ParaSight-F- Becton-Dickinson; Malaria PfTest-ICT diagnosis)	Sens: 84%-97% Spec: 81%-100% Lower values probably due to low parasite densities	□ Speed and ease of use; minimal training requirements to achieve reliable results □ No electricity, no special equipment needed; could be used at health post or community outreach □ Card format easier to use for individual tests; dipstick test easier to use for batched testing.	□ Will not diagnose non-falciparum malaria although subsequent generation tests will be able to do this □ Will not quantify parasitaemia □ Can remain positive after clearance of parasites
Light Microscopy	Optimal conditions: Sens: >90% Spec: 100% Typical field conditions: Sens: 25%-100% Spec: 56%-100%	□ Species-specific diagnosis □ Quantification of parasitaemia aids treatment follow-up	□ Requires relatively high degree of training and supervision for reliable results □ Sensitivity and specificity dependent on training and supervision □ Special equipment and supplies needed □ Electricity desirable □ Time-consuming
Fluorescent Microscopy: Acridine Orange (AO) stained thick blood smears	AO: Sens: 42%-93% Spec: 52%-93%	□ Results attainable more quickly than normal microscopy	□ Special equipment and supplies needed □ Sensitivity of AO poor with low parasite densities

Table continued

Table 2.3 continued

Method	Sensitivity/Specificity	Advantages	Disadvantages
Quantitative Buff Coat (QBC) – (Becton-Dickinson)	QBC: Sens: 89% Spec; >95%	• Speed and ease of use (takes 15 minutes to detect parasites) • Can easily detect low levels of parasitaemia as more blood is used per sample • No loss of parasites during the procedure	Electricity required Unreliable species diagnosis; non-specific staining of debris and non-parasitic cells QBC will not quantify parasitaemia Acridine orange is a hazardous material
Clinical, especially based on formal algorithm such as integrated Management of Childhood Illnesses (IMCI) or similar algorithm	Variable depending on level of clinical competency, training and malaria risk (endemicity): with IMCI Low Risk: Sens: 87% Spec: 8% High Risk: Sens: 100% Spec: 0%	Speed and ease of use No electricity, no special equipment needed beyond normal clinical equipment (thermometer, stethoscope, otoscope, timer)	Can result in high degree of misdiagnosis and over-treatment of malaria Requires close supervision and retraining to maximize reliability

Source: Wilson, M.L., et al., 2013; Bloland, P.B. WHO 2001 (Bloland, 2001, Wilson, 2013)

2.9 Major complications of malaria in under-five children

In children, severe malaria is mainly manifested by three clinical syndromes. These include severe anaemia, cerebral malaria and increased rate of and depth of breathing commonly known as Acute Respiratory Distress Syndrome (Newton, 1998). Although severe malaria is mostly attributed to *P. falciparum* (WHO, 2000a), *P. vivax* and *P. knowlesi* can also cause severe disease (WHO, 2012b). More than 90% of deaths from severe malaria result from infections with *P. falciparum (WHO, 2012b, WHO, 2000a).* The delay in seeking treatment for uncomplicated malaria is a significant risk factor for severe malaria in children (WHO, 2012b).

2.9.1 Severe Malarial Anaemia (SMA)

Initially as early as 1989, WHO defined malarial anaemia as a haemoglobin concentration of <50g l^{-1} or a haematocrit (Hct) <0.15 in the presence of a plasmodium falciparum parasitaemia >10,000 parasites μ l^{-1} with a normocytic blood film (warrell, 1989). A decade later, this definition was challenged by some researchers because of its use of a predetermined cut off point for parasitaemia which remain widely variable dependent on age and level of endemicity (Menendez, 2000b, Menendez et al., 1997). Moreover, this definition requires proper and adequate red blood cell morphology examination that may not be performed at every health facility in endemic areas due to scarce expertise. Menendez and colleagues concluded that such a definition would limit its use for the epidemiological study of malarial anaemia and the clinical management of the patients (Menendez, 2000b). This led to a more widely applied definition that states that malarial anaemia is a reduction in haemoglobin concentration or heamatocrit below the 'normal' for the age, sex and state of pregnancy, in the presence of malarial parasitaemia of any density in endemic areas (Menendez, 2000b). It is estimated that malaria and anaemia are responsible for about 40% of all under five hospitalizations and 30% of all under-five hospital deaths in Malawi (USAID, 2009). Under normal circumstances, factors significantly associated with paediatric anaemia include bacteraemia, nutritional and micronutrient deficiencies in Vitamin A and B12, hemoglobinopathies, hookworm, genetic disorders and HIV (Abdalla, 2004, Calis, 2008). Furthermore, in the presence of malaria infection, haemoglobin concentrations may reduce by between 15 and 20g l^{-1} for both sexes and all age groups in a community (Menendez, 2000a).

About 60% of anaemia episodes (Hct <0.25) is believed to arise from malaria in highly endemic areas (Menendez, 1997). The main causes of anaemia during an acute uncomplicated *falciparum* malaria is the destruction of red blood cells or decreased production of red blood cells occurring 48 hours after the onset of fever (Menendez, 2000a). These mechanisms lead to shock, impaired consciousness and respiratory distress in young children (Table 2.5**Error! Reference source not found.**) (Mackintosh, 2004).

Table 2.5: Clinical features of malaria and possible mechanisms of disease

Syndromes	Clinical features	Disease Mechanism
Severe anaemia	Shock Impaired consciousness Respiratory distress	Reduced Red Blood Cell production (reduced erythropoietin activity, proinflammatory cytokines); increased RBC destruction (parasite-mediated, erythrophagocytosis antibody and complement-mediated lysis)
Cerebral complications (Cerebral Malaria)	Impaired consciousness convulsions long-term neurological deficits	Microvascular obstruction (parasites, platelets, rosettes, microparticles); proinflammatory cytokines; parasite toxins
Metabolic acidosis	Respiratory distress, hypoxia, tachypnea; acidaemia; reduced Central Venous pressure	Reduced tissue perfusion (hypovolaemia, reduced cardiac output, anaemia); parasite products, proinflammatory cytokines; pulmonary pathology (airway obstruction, reduced diffusion)
Other	Hypoglycaemia, disseminated intravascular coagulation	Parasite products and/or toxins, proinflammatory cytokines; cytoadherence

Source: Adapted from Mackintosh, C.L., et. al. Trends in Parasitology 2004 (Mackintosh, 2004)

SMA is more prevalent in HIV-1 infected and HIV-1 exposed children. A large cohort study to determine if HIV-1 exposure and/or infection increased prevalence of SMA with acute malaria in Kenya showed that HIV-1 exposed children were twice likely to have SMA (Hb <6g/dl) than HIV-1 negative children and the risk increased by three-fold in HIV-1 infected as compared to HIV-1 negative children (Otieno, 2006). There is lack of data to confirm whether these adverse outcomes may be exacerbated by some treatments used in HIV exposed and HIV infected children such as the use of cotrimoxazole prophylaxis which is said to be associated with some haematological adverse reactions including aplastic anaemia, megaloblastic anaemia, and haemolytic anaemia (Goldberg, 1993). An understanding of such may form a basis for appropriate interventions to prevent adverse complications from malaria because even if treated in hospital, children with severe anaemia remain at a higher risk of anaemia after discharge with a 15 fold incidence of mortality compared to children who did not have severe anaemia (Phiri, 2008).

2.9.2 Cerebral Malaria

Worldwide, 19% of over half a million children under the age of five affected by cerebral malaria, die (Murphy S.C., 2001). An estimated 2% of childhood survivors of cerebral

malaria in Africa experience neurological complications including learning impairments and disabilities due to brain damage lasting more than 6 months. Cerebral malaria is defined as an unarousable coma not attributable to any other cause, with a Blantyre coma scale of ≤2 lasting for more than one hour with no other evident cause of coma (e.g. meningitis, post-ictal state and hypoglycaemia); with presence of *P. falciparum* malaria by blood film (Robert, 1996). The diagnosis of cerebral malaria is supported with the presence of malarial retinopathy on ophthalmoscopy (Beare, 2006). However, post-mortem examination of the brain either by autopsy or supra-orbital sampling remains a definitive diagnosis of cerebral malaria (Milner, 2005). Children with cerebral malaria suffer serious consequences that result from complex pathophysiological changes leading to microvascular obstruction, proinflammatory cytokines and parasite toxins. These lead to impaired consciousness, convulsions and long-term neurological challenges (Ngoungou, 2008).

2.9.3 Acute Respiratory Distress Syndrome

Signs and symptoms of respiratory distress have been observed in many African children (Murphy, 2001). Acute Respiratory Distress Syndrome (ARDS) is one of the complications of severe malaria occurring in 40% of children with severe *falciparum* malaria (Walter, 2012) but some have argued that it occurs more frequently in adults than in children (Mohan, 2008). Although it has been known to be caused by conditions such as sepsis, bacterial, viral diseases and aspiration pneumonia, evidence suggests that it also on its own present as a severe complication of severe malaria. Severe forms of *P. vivax* malaria have been associated with ARDS because *P. vivax* has the ability to immobilise chondroitin sulphate A and hyaluronic acid to a much lesser degree than *P. falciparum*. However, sequestration of parasitized erythrocytes and lung inflammatory changes in *P. falciparum* malaria are thought to result in ARDS (Walter, 2012) as well. Irrespective of effective treatment, ARDS has been associated with poor prognosis accompanied with a sharp deterioration in one's condition. This has been described to result from compensation of metabolic acidosis, noncardiogenic pulmonary oedema, concomitant pneumonia and severe anaemia (Walter, 2012).

2.10 Measures for malaria control in children

The Roll Back Malaria Partnership defines malaria control as "reducing malaria morbidity and mortality to a locally acceptable level through deliberate efforts using the preventive and

curative tools available today" (Partnership, 2008). There are many ways to achieve this. Prevention and control with the use of ITNs, IRS and case management remain the effective malaria control strategies in both adults and children (Partnership, 2008). The use of chemoprevention for malaria is presently recommended in both pregnant women as Intermittent Preventive Treatment in pregnancy (IPTp), in infants as Intermittent preventive Treatment in infants (IPTi) and Seasonal Malaria Chemoprevention (SMC) formerly known as Intermittent Preventive Treatment in children (IPTc) in resource limited settings (Kayentao, 2013, WHO, 2013b).

2.10.1 Use of chemoprevention to control malaria in children

Intermittent Preventive treatment in infants and Seasonal Malaria chemoprevention are the two main strategies for malaria chemoprevention in children.

2.10.1.1 Intermittent Preventive Treatment in infants

IPTi is recommended for all infants at risk of *Plasmodium falciparum* infection in sub-Saharan African countries with moderate-to-high malaria transmission and low levels of parasite resistance to SP (WHO, 2010e). The implementation follows the already existing immunisation services in the Expanded Programme for Immunisation (EPI) in that it is administered at defined intervals corresponding to immunisation schedules DPT2, DPT3 and Measles vaccine. However, despite the ease of implementation and cost-effectiveness of this intervention, the 2013 World Malaria report indicates that only Burkina Faso has adopted this as a national policy following WHO recommendation in 2009 (WHO, 2013b). It is not clear yet whether this lack of wide-scale implementation of this intervention is resulting in concerns about the impact of resistance to SP. For example, a large double-blinded placebo controlled trial in Tanzania, compared three different drugs used as IPTi in children. These drugs were Mefloquine, SP and a combination of chlorproguanil and Dapsone. A 38% protective efficacy against malaria in infants was demonstrated with mefloquine, a long acting efficacious drug while SP and Chlorproguanil-Dapsone were not efficacious (Gosling, 2009). The protective efficacy of Mefloquine was high immediately following administration of the treatment and rapidly waned off. A secondary analysis of trials on ITPi in Tanzania established that the protective efficacy of Mefloquine was not sustainable beyond 2 months after the third dose (Cairns, 2010). More sustained and high efficacy chemoprevention

options therefore need to be explored. However, in a pooled analysis of six IPTi-SP trials use of SP for IPT in infants showed a protective efficacy of 30.3% against clinical malaria and 38.1% against hospital admissions associated with malaria parasitaemia during the period that the children received the treatment (Aponte, 2009).

2.10.1.2 Seasonal Malaria Chemoprevention

Seasonal Malaria chemoprevention (SMC) refers to "administration of full treatment courses of an effective antimalarial medicine during the malaria season to prevent malaria illness in children aged 2-59 months (WHO, 2012c). This intervention is most effective in Africa's Sahel sub-region where amodiaquine plus SP are effective. SMC in this region has a more than 65% protective efficacy against malaria in young children under the age of five (**Error! Reference source not found.**). It is not known yet whether there is a correlation between the high efficacy levels and prevalence of antifolate resistance as there is limited data to corroborate these findings with country specific prevalence of antifolate resistance in this region. A meta-analysis of reported *dhfr* and *dhps* mutant genotype frequencies in African Plasmodium parasite populations reported a 3% prevalence of the *dhps* double mutant genotype in this region compared to 44.3% in East Africa (Sridaran, 2010). Pearce *et al* have recently shown significant increase in *dhfr* but not *dhps* mutations in areas where IPTi was implemented in Tanzania (Pearce, 2013). Nonetheless, more countries in this region are currently in the process of finalizing the adoption of SMC as policy (WHO, 2012c).

Table 2.6: A summary of studies on Seasonal Malaria Chemoprevention in Africa

Author (year)	Country	Malaria transmission	SMC	Age of children	Protective Efficacy (95% CI)	References
Cisse, B (2006)	Senegal	Seasonal	AS and SP (given at 3 occasions during malaria transmission season for a duration of 3 months)	2-59 months	86% (80%-90%)	(Cisse, 2006)
Dicko et al (2008)	Mali	Highly seasonal	SP administered at two occasions at monthly intervals	<5years and >5 years	<5years old: 42.5% (28.6%-53.8%) >5years old: 35.9% (11.8%-53.4%)	(Dicko, 2008)
Kweku (2008)	Ghana	Intense with two seasonal peaks	Arm 1: SP bimonthly Arm 2: AS+AQ monthly Arm 3: AS+AQ bimonthly	3-59 months	AS+AQ Monthly group: 69% (63%-74%) SP group: 24% (14%-33%) AS+AQ group: (6%-27%)	(Kweku, 2008)
Dicko (2011)	Mali	Highly seasonal	SP and AQ (given at 3 occasions, monthly intervals)	3-59 months	82% (78%-85%)	(Dicko, 2011)
Konate (2011	Burkina Faso	High transmission but seasonal	SP +AQ Placebo (monthly intervals during peak malaria transmission)	3-59 months	IRR clinical malaria: 0.29 (0.26%-0. 32%)	(Konate, 2011)
Bojang (2011	The Gambia	Highly seasonal	SP Single dose AQ Single dose	6 years and under	RD 1.6 (0.24-3.5)	(Bojang, 2011)

AS: Artesunate, SP: sulfadoxine pyrimethamin, AQ: Amodiaquine, IRR: Incidence rate Ratio, RD: Risk Difference

2.10.2 Use of Insecticide Treated bed-nets

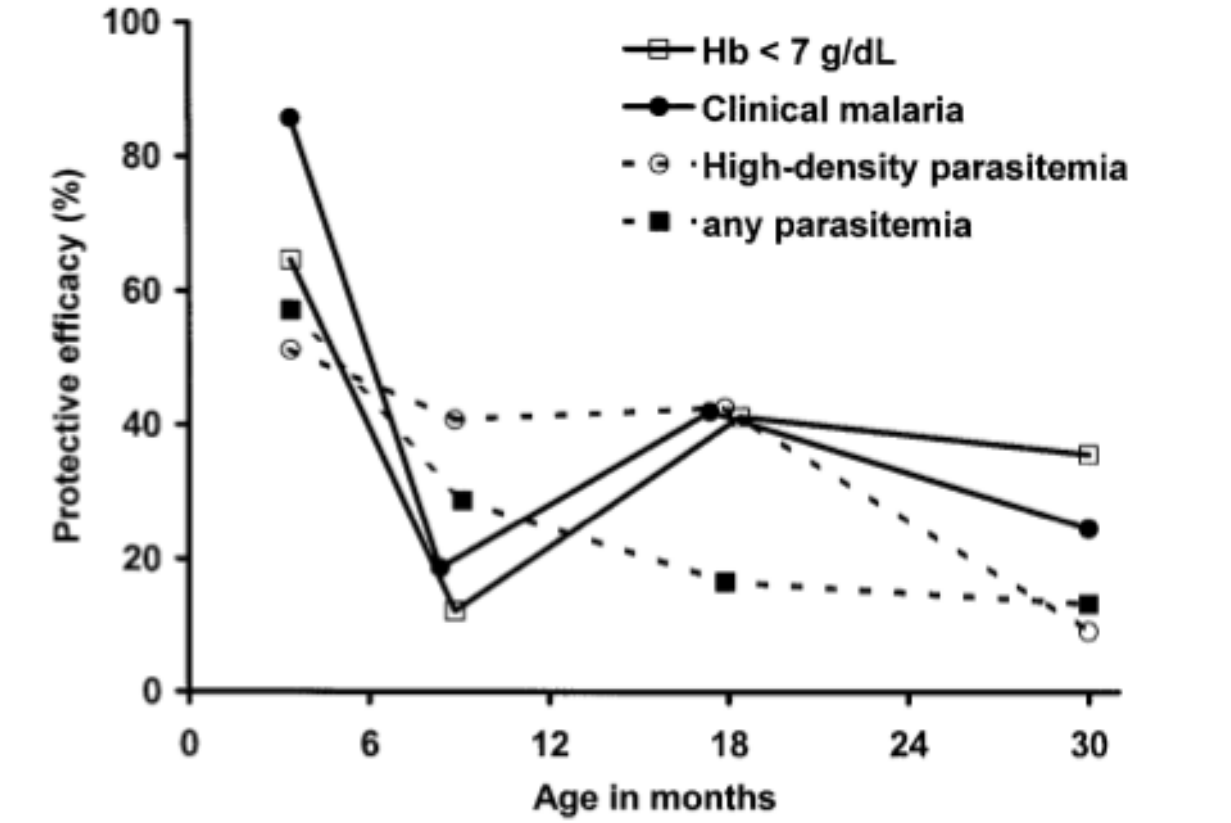
The use and effectiveness of ITNs in reducing the malaria burden has been demonstrated in many settings of diverse malaria transmission patterns. There are two forms of ITNs: Conventional ITNs which require re-treatment with insecticides at determined intervals and Long Lasting Insecticide Nets (LLINs) which are treated with insecticides at source by the manufacturers. These do not require re-treatment with insecticides until they outlive their lifespan (WHO, 2013b). Although ITNs had been previously thought of mainly providing personal protection, there is increasing evidence that high coverage of ITNs within a community produces mass effect and therefore its effect in reducing transmission is community-wide than individual (Hawley, 2003). Since most of the important vectors for malaria transmission in humans in Africa bite at night and in early hours of the morning (WHO, 2013a), with few biting earlier, they are susceptible to ITNs but huge impact in reducing malaria prevalence of more than three fold is achieved where *Plasmodium ovale* and *Plasmodium malariae* are common compared to *P. falciprum* (ter Kuile, 2003). A pooled analysis of five trials by Lengeler *et al* examined the effect of ITNs on all cause child mortality from all areas of stable malaria transmission in SSA and showed a protective efficacy of 18% and a 50% reduction in the incidence of clinical episodes for both *P. falciparum* and *P. vivax* respectively (Lengeler, 2004) demonstrating the high efficaciousness against *P.vivax*.

2.10.2.1 ITNs and IRS used in combination for the control of malaria

Eisele, T *et al*, applied the LiST model which is used to estimate the number of child malaria deaths that can be prevented from scale-up of malaria prevention interventions in *P. falciparum* settings (Eisele, 2010). With their model, they were able to show that a combination of ITNs and IRS reduce malaria attributable mortality in children aged 1-59 months by 55%. The LiST model assumes that increases in the coverage of an intervention result in a reduction of one or more cause-specific deaths or in reduction of a risk factor (Eisele, 2010). The synergistic effect of the joint use of ITNs and IRS has also been shown in many studies in sub-Saharan Africa (Fullman, 2013, Hamel, 2011, Pinder, 2011, Kleinschmidt I., 2009) although there is strong argument to the contrary suggesting that it is

difficult to isolate the effect of ITNs and IRS on malaria control in situations where other interventions such as use of artemisinin combination therapy, larviciding, environmental management and heath education are also in use (Bhattarai, 2007, Over, 2004, Okumu, 2011). Researchers in Eritrea have argued that there is no added advantage of using the two interventions in combination because their nature of indoor use targets the same malaria vectors that tend to rest inside the house before or after taking a blood meal (Nyarango, 2006). On the other hand, IRS appears to be most effective when it is used alone in medium to low transmission areas compared to when it is used in high transmission areas (Fullman, 2013). Other than all-cause child mortality and malaria-specific mortality, ITNs are highly efficacious against clinical malaria, anaemia and any parasitaemia from the age of 6 months (ter Kuile, 2003) as **Figure 2.3** below for an area with intense perennial transmission in western Kenya illustrates.

Figure 2.3: Protective efficacy of insecticide-treated bed nets by age



Source: ter kuile, F.O., et al., Am. J. Trop. Med. Hyg., 2003 (ter Kuile et al., 2003)

2.10.3 Other Vector control strategies

2.10.3.1 Larviciding

In 2012, WHO issued an interim position statement on use of larviciding for malaria control. Larviciding which WHO defines as the "regular application of chemical or biological agents to kill the mosquito larvae or create a situation which is unfavourable for mosquito breeding" (WHO, 2012a), was first used in the 1930's and 1940's in Brazil, Egypt and the copper mines in Zambia (WHO, 2012a, Killeen, 2002). In Zambia, water management with larvicides and drainage reduced malaria mortality, morbidity and incidence by 70-95% within few years and the protective efficacy of this intervention was sustained for two decades (Killeen, 2002). In

Brazil, rigorous measures of larval control were employed when part of the country was infested with *An*. *gambiae* which claimed the lives of hundreds of people. During this time, a well-organized rigorous campaign was launched where all small water bodies preferred by *An*. *gambiae* were searched and larvicides applied. This was complemented by other methods that targeted the adult mosquito. Within two years, the *An*. *gambiae* was eradicated in this area (Killeen, 2002). The same methods effectively eradicated the *An gambiae* in Egypt in the early 1940s (Killeen, 2002). However, despite these historical pieces of evidence, WHO does not give a straightforward recommendation on the use of larviciding for malaria control in sub-Saharan Africa largely because of its inability to effectively target all the larval breeding sites which are so numerous and changing from one time to the other (WHO, 2012a). Killeen *et al* however argue that bed nets and clinical management alone are not enough to effectively control malaria as they face a lot of challenges in terms of distribution and utilization but also the ever changing behaviour of human biting mosquitoes (Killeen, 2002). As such other malaria control strategies would complement the current ones for better results.

2.10.3.2 Environmental Management

An internationally recognized definition of Environmental Management (EM) by WHO puts in to context the use of this strategy for malaria control. WHO defines EM as "the planning, organization, carrying out and monitoring of activities for the modification and/or manipulation of environmental factors or their interaction with man with a view to preventing or minimizing vector propagation and reducing man-vector-pathogen" (WHO, 1982). In a systematic review of studies covering two centuries, all but one study reported protective efficacies on clinical malaria parameters that ranged from malaria hospital admission, malaria related deaths, malaria morbidity, spleen rate and malaria incidence of 79.5%-88.0% (Keiser, 2005). In these studies, the mostly used EM strategies were environmental modification which created sustained effect on land, water or vegetation to reduce malaria control; environmental manipulation which was temporary in nature whereby unfavourable conditions for the vector were created and human habitation was modified (Keiser, 2005). It has been argued that the study that did not show any protection from EM, used improper methods in the implementation of the programme (Keiser, 2005). Although most of these studies were done a long time ago and difficult to verify the methods used and whether simultaneous use

of other malaria control interventions like ITNs and chemoprevention could likely have affected the results, EM is a promising complimentary strategy for sustained malaria control in malaria endemic regions.

2.10.4 Malaria Case Management in children

Adequate case management of malaria patients is an integral part of malaria control. Delays in accessing prompt and effective treatment result in fatal consequences in vulnerable populations like the under-five children (Velema, 1991). Management of malaria mostly in under-five children starts at home with a caregiver either giving an anti-malarial or an antipyretic (Velema, 1991) before seeking care at the hospital. Currently ACTs are considered the recommended treatment for uncomplicated malaria in both adults and children replacing choloroquine and sulfadoxine pyrimethamine which were rendered ineffective as a result of increased resistance which contributed to significant mortality (Frosch, 2011). A clinical diagnosis of malaria in under-five children is sufficient for an ACT prescription in high transmission areas whereas for older children and adults, a definitive parasite based diagnosis is a prerequisite (WHO, 2006c, WHO, 2005a).

2.11 Uptake of malaria control interventions in children

In most malaria endemic areas, the uptake of malaria control interventions has remained low despite available evidence showing that they are effective (Hanson, 2004). There is paucity of data on factors directly linked to uptake of these interventions in children. However, in pregnant women, personal attributes such as educational level, marital status, knowledge about the interventions, gravidity, and health facility factors like distance to the health facility, unavailability of services and poor quality of services at the health facility are highly associated with uptake of malaria control interventions (Mutulei, 2013). In a report by the Medicines for Malaria Venture (MMV) the author cites the continual use of non-recommended antimalarials to treat children including monotherapies as barriers to uptake of paediatric medicines (MMV, 2013). Since children are under direct care of their parents and caregivers, adult-related factors such as above could be used as proxy measures for determining factors that influence the uptake of malaria control interventions in these children.

In Malawi, the uptake of various malaria interventions has been generally poor. According to the 2012 Malaria Indicator Survey (MIS) report (Programme, 2012), only 32% of households owned one or more insecticide treated nets and 56% of children under-five slept under a net in the previous night. Coverage of IPTp is relatively high for the region with 77% of pregnant women receiving one dose of SP (Programme, 2012). However, only 54% of pregnant women received the recommended two doses in Malawi. As a result, malaria still remains an important cause of morbidity and mortality in this country (MoH, 2005a).

2.12 Sulfadoxine – Pyrimethamine and Cotrimoxazole cross-resistance

SP and cotrimoxazole also known as sulfamethoxazole-trimethoprim share a similar chemical structure. Since they both provide their antimicrobial action through inhibition of the same enzymes in the folic acid biosynthetic pathway (pyrimethamine and trimethoprim inhibit dihydrofolate reductase, whereas sulfadoxine and sulfamethoxazole inhibit dihydropteroate synthetase), cross-resistance could develop, and a decrease in the antimalarial efficacy of cotrimoxazole may occur in parallel with SP resistance development (Iyer et al., 2001, Feikin et al., 2000). A study in Malawi that investigated the efficacy of cotrimoxazole in treating malaria found similar cure rates with SP (adequate clinical and parasitological responses of 87.2% and 80% respectively) (Hamel et al., 2005). Laufer *et al* (Laufer et al., 2006) have also shown the potential of return of efficacy of the antimalarial chloroquine after a few years of it not being used. It is not known if the removal of the use of SP for the first line treatment of malaria in the general population could have reduced the degree of resistance of *P. falciparum* to cotrimoxazole.

2.13 Malaria rebound

Malaria rebound could be referred to as a hypothetical overshot that could occur in populations that have lost their immunity (Coleman, 1999).

2.13.1 The risk of malaria rebound with the use of malaria control measures such as ITNs

The use of malaria control interventions such as insecticide treated bed nets only provide partial reduction in exposure to malaria such that those people sleeping under ITNs would still experience mosquito bites but less frequently compared to those not using ITNs (Coleman, 1999). Since acquisition of natural immunity in young children is dependent on the number of subsequent infective mosquito bites (Doolan, 2009), the protective nature of ITNs is suggested to reduce the rate at which effective immunity to malaria is attained in ITN users (Coleman, 1999, Kariuki et al., 2003). There have been suggestions that marked transmission reductions areas with high malaria transmission may result in a delay in the acquisition of protective immunity and a consequent shift in the epidemiological profile of malaria with an increase in the average age at which children develop severe forms of malaria and also the prominence of cerebral malaria (Coleman, 1999, Snow and Marsh, 2002).

2.13.2 Malaria rebound after stopping malaria chemoprophylaxis

Similarly, there is concern that children who receive sustained malaria protection are at a higher risk of malaria morbidity and mortality once the protection is stopped. In one study, Gambian children who had received variable malaria chemoprophylaxis over most of their first 5 years of life were followed up for 5 years (Greenwood et al., 1995). The risk of clinical malaria during the first year after stopping pyrimethamine–dapsone was significantly higher in children who had received chemoprophylaxis. A rebound effect was also observed in a study in Tanzania where infants between 2 and 12 months of age were given weekly pyrimethamine-dapsone. After the end of the intervention period, infants who received chemoprophylaxis had almost doubled rates of severe anaemia and malaria during the following year than those who received a placebo (Menendez et al., 1997). A summary of studies showing malaria rebound effects after termination of a malaria chemoprophylaxis is presented in **Table 2.7Table 2.7** below.

Some beneficial effects after termination of malaria chemoprophylaxis were observed in some parts of Africa in the 1950's where regular drug administration for up to 2 years in school children did not interfere with pre-existing immunity and termination did not create additional

risk (Menard, 2003). This might have resulted from the acquired immunity to malaria in older children compared to infants who are immune naïve. Furthermore, the use of IPTi-SP in different settings in Africa was also not associated with rebound effects after treatment was stopped (Aponte, 2009). It is likely that this resulted from the incomplete and interim nature of the protection provided by IPTi because of the interim nature of the intervention which leaves children unprotected in between rounds, including for a 4 to 6 months of exposure prior to the last course of IPTi at 9 months of age.

Daily CPT however may provide more complete protection from malaria. This is because cotrimoxazole has been found to offer antimalarial effects in several studies (Sandison, 2011, Kamya et al., 2007, Gasasira et al., Thera et al., 2005). Without adequate exposure to malaria during the first year of life, infants do not have a chance to develop a significant degree of naturally acquired immunity. Therefore, children receiving **daily** CPT from birth to 14 months may have a higher risk of malaria after it is stopped.

Table 2.7: Studies showing malaria rebound effect after termination of drug treatment

Drug used (country)	Ages of study group	Duration of treatment	Duration of post-intervention follow-up	Effect on malaria morbidity	Rebound effect
P-D[1] (Tanzania)	2 mo. at start of study	Weekly for one year	One year after termination of treatment	Reduced incidence of clinical malaria by 40% during treatment period	80% higher incidence of clinical episodes in treated group during the year following termination of treatment
P-D (The Gambia)	3 mo. at start of study	Every 2 weeks for maximum of 5 years	5 years	65% reduction in malaria episodes after 3 years of chemoprophylaxis	52% more cases in treated group during the year following termination of treatment
SP[2] + artesunate (The Gambia)	Entire villages, all ages	MDA[3] 1 dose	20 weeks	Reduced rate of malaria attacks in children <11 yr by 60%	Rate of clinical malaria was 69% higher in treated groups 3 months after treatment
SP (Mali)	3 mo. to 20 years	MDA 1 dose	24 weeks	Reduced incidence of first malaria episode from 26% to 3% during first month	Incidence of first malaria episodes in treated group rose to 42% compared to 17% (untreated group) during the third month after treatment

[1]P-D: pyrimethamine-dapsone; [2]SP: sulfadoxine-pyrimethamine; [3]MDA: mass drug administration

Source: O'Meara, W.P., et al., 2005, Malaria Journal

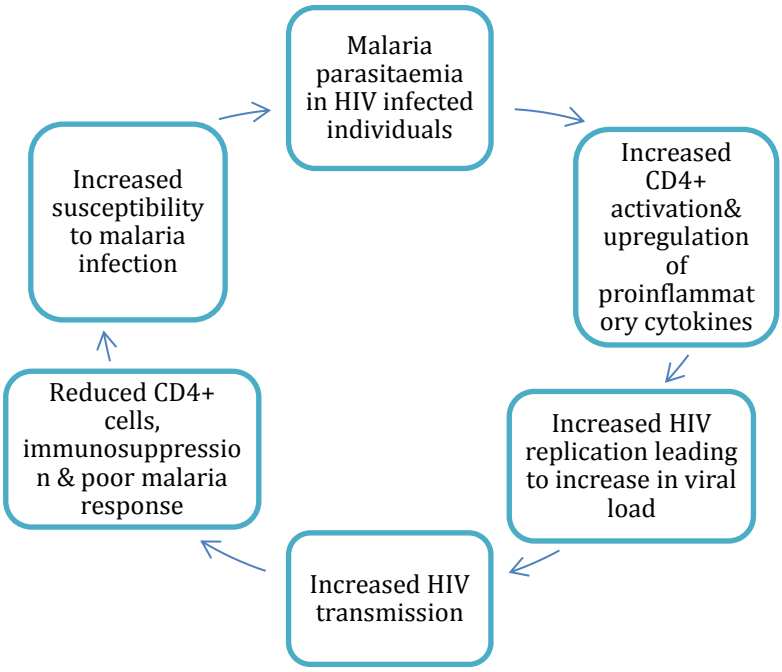
2.14 Malaria and HIV Co-infection

Both HIV and malaria have greatly affected sub-Saharan Africa. These diseases have a wide overlap in geographical distribution resulting in co-infection in that those with HIV have frequent episodes of malaria and malaria increases HIV plasma viral load (Kublin, 2005a). There is evidence that during a febrile malaria attack, there is a one-log increase in viral load in HIV infected patients in their chronic stage (Table 2.8) (Kublin, 2005b) and on the other hand, HIV infection significantly increases susceptibility to malaria infection (Patnaik, 2005). Further, an 8% increase in the peak of the HIV epidemic and a 13% increase in the peak of malaria is seen in the presence of interaction between the two diseases (Abu-Raddad, 2006). In HIV infected pregnant women, both placental and peripheral malaria parasitaemia are significantly associated with higher placental viral load (Mwapasa, 2004). This increased viral

load is suggested to be an important factor in the transmission of HIV from mother-to-child, with more transmission occurring when the viral load is high. It is estimated that more than 50% of women with high viral load of greater than 50,000 RNA copies/ml, transmit the virus (Thea, 1997, Fang, 1995) at a 6-fold transmission rate compared to those with undetectable viral load (Thea, 1997).

A study of HIV-infected but treatment naïve children aged between 25-59 months admitted with malaria in Kenya showed that HIV infection significantly modified the age-dependent acquisition of malaria-specific immunity and reduced the extent of IgG response to merozoite antigens (Muema, 2011). There is also evidence that malaria parasitaemia in HIV infected individuals, is associated with increased activation of CD4+ cells and up regulation of proinflammatory cytokines (Alemu, 2013). This process increases the number of susceptible cells that are targeted by HIV-1 infection such that an increase in the number of target cells will also increase the viral load (Alemu, 2013). On the other hand, these CD4+ cells play a pivotal role in the immune response to malaria. Their availability is essential to help B cells produce the antibody that is important for parasite clearance (Langhorne, 2006). They also produce cytokines that rapidly increase the phagocytic and parasitological response of the innate immune system, and diminish this response later on to minimize immunopathology (Langhorne, 2006). The consequences of HIV and malaria co-infection can be summarized by a vicious cycle of successive pathophysiological processes presented in Figure 2.4. In the absence of any interventions, these events may constantly repeat themselves resulting in more infections and deaths.

Figure 2.4: A diagrammatic presentation of the vicious cycle of HIV and malaria co-infection



The lowering of CD4+ cell levels increases parasitaemia in children and deteriorates their clinical status. In more advanced HIV disease where immunosuppression is more pronounced, the frequency of malaria episodes and malaria parasite densities increases (Chaisavaneeyakorn, 2002). This results from minimal malaria-specific antibodies which diminish in numbers as the HIV disease advances (van Geertruyden, 2009). Low levels of CD4+ cells and high amount of HIV viral load in mothers of HIV infected and HIV exposed children leads to doubling of severe morbidity and early mortality in the children (Dunne, 2003). HIV-1 alone has been found to be an important risk factor for the increase in parasite density in HIV infected children less than five years old with cerebral malaria (Imani, 2011a). An additional 3 million cases of malaria and 65 thousand malaria related deaths annually are estimated to be as a result of the impact of HIV (WHO, 2008, UNAIDS, 2007b). The resultant rates of HIV and malaria co-infection and interactions between the two diseases pose major public health problems. Generally, people living with HIV experience a higher incidence of malaria and increased parasitaemia than those not infected mainly resulting from

the HIV immunosuppression that is believed to speed up the rate of parasite maturation in the liver and causes alteration of the course of the disease leading to a severe form of disease in those with malaria (Imani, 2011b). Clinical malaria treatment failure in these patients has been attributed to decreased ability to clear drug resistant parasites as a result of HIV (UNAIDS, 2007a). Greater understanding of interactions between HIV and malaria interventions is key to unlocking their potential in preventing morbidity and mortality. In recent studies, Protease Inhibitors like Lopinavir-ritonavir have shown to dramatically lower the incidence of malaria after treatment with artemether lumefantrine (Achan, 2012). Lopinavir-ritonavir, leads to the inhibition of lumefantrine which would extend the post-treatment prophylactic effect or antimalarial synergy between lumefantrine and lopinavir (Achan, 2012). Studies by the ACT Consortium are on going to elucidate the drug-drug interactions between the two diseases (Consortium., 2013). Table 2.8 is a summary of assumptions related to the interaction of HIV and malaria co-infection. A log increase of 0.82 in HIV viral load level is seen with malaria infection in the chronic stage of HIV compare to a log increase of 0.08 in the absence of clinical malaria (Abu-Raddad, 2006). Furthermore, susceptibility to malaria infection in HIV-1 infected people is enhanced by 103% during the advanced stage compared to 0.4% in the chronic stage (Abu-Raddad, 2006).

Table 2.8: The core assumptions of HIV/Malaria interaction model

Assumption	Parameter Value
Logarithm increase in HIV viral load level during malaria infection:	
Acute stage	0
Chronic stage with clinical malaria	0.82
Chronic stage with non-clinical malaria	0.08
Advanced stage	0.2
Susceptibility enhancement to malaria infection in HIV-1 Infected people:	
Acute Stage	0.00%
Chronic Stage	0.44%
Advanced Stage	103%
Duration of heightened viral load during malaria episodes	42 days
Fractional reduction in sexual activity during malarial malaria infection:	
Clinical	10%
Non-clinical	3%
Fraction of malaria infected patients developing clinical malaria	
HIV negative	16%
HIV positive	31%
Enhanced HIV mortality in dually infected patients	
Areas of stable transmission	0.00%
Areas of non-stable transmission	25%

Source: Abu-Raddad et.al. 2006 (Abu-Raddad, 2006)

2.15 The burden of HIV in sub Saharan African children

HIV continues to pose enormous public health challenges worldwide. According to the UNAIDS report on the update of HIV epidemic, seventy per cent (70%) of the 35.3 million people living with HIV, are in sub Saharan Africa (UNAIDS, 2013b). Malawi is at the epicentre of the epidemic that is responsible for eight deaths every hour (Bello, 2006). Out of a population of nearly 15 million, almost 1.1 million people in Malawi were living with HIV at the end of 2012 (UNAIDS, 2013c). The majority of HIV infections occur through heterosexual sex and women are more affected by HIV than men (Bello, 2006). Several explanations have been suggested on why women are the most vulnerable. Although a study in Uganda in the early 21st century did not find any differences in the per act transmission of HIV from man or woman to the uninfected partner (Gray, 1994), many studies in both the

developed and undeveloped world have reported an efficient transmission of HIV from a man to a woman compared to the other way round (Royce, 1997). Use of normal contraceptives more especially injectables has been linked to increase in the acquisition of HIV among HIV negative women. Women on injectable contraceptives also tend to have higher genital HIV-1 RNA concentrations compared to women on other contraceptives or not on contraceptives (Heffron, 2012, Lavreys, 2004). Other factors such as anal sex, vaginosis, use of intrauterine devices and low CD4 counts of a male sexual partner have been suggested to increase women's susceptibility to HIV (Lazzarin, 1991, Taha, 1998, Nicolas, 1994).

2.16 The Epidemiology of Mother to child transmission of HIV

Most of the HIV incidence (i.e. newly acquired infections) occur among young people, particularly those between the ages of 13 and 24 years when they become sexually active (Bello, 2006). HIV may be transmitted in utero, during labour and through breast-feeding to infants (WHO/UNAIDS/UNICEF/UNFPA, 2003). Recently, 260,000 children in low and middle-income countries became newly infected with HIV through mother-to-child transmission, down by 35% from 2009 (UNAIDS, 2013b). The 2003 Joint WHO and UN report shows that without any intervention, 27-30% of children born to HIV infected mothers will acquire the virus (WHO/UNAIDS/UNICEF/UNFPA, 2003) with a transmission rate of 5-10% during pregnancy, 10-20% during labour or 5-20% during breastfeeding (Cock, 2000, Raisler, 2005). Most transmission takes place in late pregnancy and during delivery compared to early pregnancy (Newell, 2001). However, post-natal transmission as a result of breastfeeding substantially contributes to the overall risk of mother to child transmission of HIV (Newell, 2001). Maternal HIV disease progression is highly associated with vertical transmission of HIV from mother to child more especially HIV infected pregnant and breastfeeding women with high HIV viral load and low CD4+ counts are more likely to transmit the virus to their children compared to those with low viral load and high CD4+ count (Ruiz, 1998). Duration of membrane rupture has been shown through a meta-analysis of fifteen cohort studies to increase the risk of HIV transmission and is more prevalent among premature infants (Group, 2001). Irrespective of CD4 count, viral load and whether the woman is on antiretroviral drugs; delivery by elective caesarean section has been significantly

associated with a 50% reduction in the risk of HIV transmission from mother to child (Study, 1999, Ioannidis, 2001).

2.17 The natural history of the HIV disease in children

In the absence of any intervention, children with HIV infection acquired through MTCT experience a rapid evolution of the disease compared to adults with a mean survival range of 6 to 8 months with only 70% of children reaching the age of six (Ruiz, 1998). It is postulated that children (15-20%) who acquire the virus early during pregnancy develop severe immunodeficiency with opportunistic infections and encephalopathy in the first year of life and die within the first three years (Ruiz, 1998). However, those (80-85%) who acquire the virus late in pregnancy experience a slow disease progression and live for several years (Ruiz, 1998). The evolution of HIV in children is said to be strongly influenced by both maternal and infant factors such as severity of maternal disease and development of opportunist infections in the child which are believed to influence the acquisition of opportunist infections or death in the early years of life and overall progression of the disease respectively (Ruiz, 1998). All children born to HIV infected mothers (HIV exposed children) are recommended to have HIV virological testing at 4-6 weeks of age or at earliest encounter with health care professionals (WHO, 2010a) as serological tests may not accurately diagnose HIV due to circulating maternal antibodies. At the age of 9 months, a repeat HIV test is performed mostly tailored with the immunizations at 9 months (WHO, 2010a). .

A recent WHO recommendation promotes initiation of ART irrespective of immunological status or WHO clinical staging for all infants diagnosed with HIV in the first year of life and for all HIV infected children between the age of 12 and 24 months (WHO, 2010a). Although WHO recommends that CD4 should be measured at the time of HIV infection and every six months thereafter or prior to initiating ART (WHO, 2010a), this has been a challenge in resource poor settings due to limited capacity (Peter, 2008). However, monitoring of haemoglobin level is required at the initiation of ART and at 8 weeks after initiation of Zidovudine (AZT) (WHO, 2010a).

2.18 The impact of maternal CD4 and viral load in HIV exposed infants

Despite successful gains achieved from effective PMTCT interventions in reducing new HIV infections in children, concern arises regarding the health of HIV exposed infants. There have been reports from the Caribbean, South Africa, South East Asia and Europe concerning an increase in the morbidity and mortality resulting from infectious diseases among HIV exposed children (Marinda E, 2006, Shapiro RL, 2007, Mussi-Pinhata MM, 2007, Fulforf T-A, 2012, horne C, 1997). Compared to the general population and non-HIV exposed children, an increase in new neonatal infections, neonatal sepsis, acute gastroenteritis, hospitalization, post-operative complications and neonatal sepsis has been reported in HIV exposed children (Singh HK, 2011, Taha TE, 2000, Epalza C, 2010, McNally LM, 2007, Slogrove A, 2012). This is partly explained by chronic maternal infections during pregnancy which can significantly interfere with infants immune response to future infections irrespective of the vertical transmission of pathogens. Infants born to mothers with HIV viral load as high as more than 1,000 copies per ml have been observed to have decreased relative as well as absolute CD4+ T counts at 2 and 6 months of age compared to their counterparts born to mothers with undetectable HIV viral load of less than 50 copies/ml (Kuhn, 2002, Faye, 2007). A study in Malawi found reduced CD4 percentage at one month of age in HIV exposed children compared to non-HIV infected counterparts (Moraleda, 2014). Available evidence suggests a greatly increased placental production of inflammatory cytokines; tumor necrosis factor alpha and interleukin 8 among HIV infected women treated with ART than in HIV uninfected women (Economides, 1998). However, HIV infected mothers with high HIV viral load have been observed to generate higher levels of the pro-inflammatory cytokines Interferon gamma and Tumor necrosis factor alpha which is thought to remain high in women with high viral load thereby potentially driving the differences in CD4 counts in newborns (Economides, 1998) consequently increasing their risk of HIV opportunistic infections.

2.19 Transfer of maternal immunity and its implication on the HIV disease in the child

The scaling up of anti-retroviral distribution and other interventions around childbirth, has been associated with a reduced incidence of paediatric HIV infection and disease (UNAIDS, 2013a). When given to the mother during pregnancy, anti-retroviral drugs induce a direct drug

effect on maternal viral replication resulting in decreased HIV RNA in maternal circulation as well as genital secretions and significantly improves the CD4+ cell counts (McGowan, 2000). The increase in uptake of ART among HIV infected women in 2012, contributed to a reduction of 35% in new HIV infections among children in the same year (UNAIDS, 2013a). This leads to increased numbers of HIV 'exposed' children, because as the adult HIV population remain healthier and lives longer (Bello, 2006), they reconsider childbearing (Myer, 2010). At a minimum, maternal HIV antibody is present in the child's blood for the first six months of life (de Moraes-Pinto, 1996). Sometimes after six months, levels of maternal antibodies fade and most children who are not infected test negative for the HIV antibody test by 12 months of life (de Moraes-Pinto, 1996). Occasionally, it takes HIV uninfected children as long as 18 months to lose maternal antibodies (Rabkin, 2005). These children, despite not being infected with HIV, have an increased susceptibility to HIV opportunistic infections resulting from a compromised maternal immune system caused by HIV in the mother, which may lead to reduced transplacental transfer of antibodies to the foetus in utero (Moraes-pinto, 1996). At birth, HIV exposed children are challenged with increasing numbers of virulent congenital or maternally acquired neonatal infections because of increased shedding and higher pathogen levels related to immunosuppression in HIV infected mothers (Moraes-pinto, 1996). This likely interferes with the ability to adequately support development of infant immune capacity and viral exposure of the foetus in utero resulting in reduced capacity of the infant himself to fight common infections (Chougnet, 2000b, Clerici, 2000). These immunological deficiencies also interfere with the levels of immunoglobulins present in breast milk which are important in protecting infants against infections (Thomas, 2004). In the absence of any form of treatment, HIV infected children have a 2 year median survival (Dunn, 2003) with significantly higher mortality at all ages than their HIV exposed but not infected counterparts (Brahmbhatt, 2006) although when compared with non-HIV exposed children, HIV exposed, but uninfected children have a 16% higher mortality (Brahmbhatt, 2006). Severe morbidity and early mortality in HIV infected and HIV exposed children more than doubles when maternal CD4+ cell counts are low and HIV RNA is high (Brahmbhatt, 2006). Without any mitigating interventions these children experience high fatality rate of between 40-90% from PCP, a severe form and rapidly progressive pneumonia (Rabkin, 2005) that generally occurs between 3 and 6 months of life,

often as the first sign of HIV infection and before child is definitively determined to be HIV infected (Rabkin, 2005).

2.20 Prevention of Mother-to-Child Transmission of HIV in Malawi

In Malawi, all children under 24 months are actively screened for HIV exposure most especially those who present with sickness to under five clinics, the Out-Patient Department (OPD), nutritional rehabilitation unit and paediatric ward (MoH, 2014). Children born and/or breastfeeding from HIV infected mothers are immediately enrolled in the HIV Care clinics and tested for HIV using DNA-PCR from the age of six weeks in order to detect perinatal HIV infection and allow early initiation of ART (MoH, 2014). After the first HIV test at six weeks, HIV exposed children are seen on a monthly basis until the age of 6 months. Thereafter, they are seen every 3 months until they are 24 months of age. However, the scheduling of visits is determined by the health of the child (MoH, 2014). A negative HIV rapid test obtained at 6 weeks after stopping breastfeeding is a determinant for stopping routine follow-ups for these children. At twelve and 18 months, a repeat HIV test using an antibody test is done to rule out HIV infection since most children breastfeed up to 24 months (MoH, 2011a). During the period the children are being monitored, they receive daily CPT for prevention of HIV opportunistic infections.

Malawi introduced Prevention of Mother-to-Child Transmission (PMTCT) of HIV interventions as a primary preventive intervention for transmission from mother to child in 2003 using single-dose Nevirapine (NVP) as the primary ARV prophylaxis regimen used to prevent paediatric HIV infections (MoH, 2008). Although uptake of PMTCT interventions was low by women who needed it, 64% of the 544 health facilities were providing PMTCT services by 2007 (MoH, 2008). Lack of partner involvement and fear of stigma and discrimination were some of the reasons observed as deterrents to uptake of these interventions by HIV infected pregnant women (Chinkonde, 2009, MoH, 2008). In line with 2006 WHO PMTCT recommendations, the government of Malawi in 2007 introduced combination ARV prophylaxis regimen to further reduce the risk of MTCT of HIV (MoH, 2008). In its guidelines released in 2008, all HIV pregnant women who met the criteria for starting ART as per WHO Clinical staging and CD4+ count (WHO Clinical stage 3 & 4 or

WHO Clinical stage 1 & 2 with a CD4 count of <250) were started on combination ART of AZT/3TC/NVP. Infants born to women on ART were given a four weeks course of AZT twice a day (MoH, 2008). For those HIV infected women not on routine ART, single dose NVP was provided at 16 weeks gestation irrespective of their clinical stage and CD4 count. This was accompanied with instructions to take at the onset of labour. In addition, the women were started on a twice-daily dose of AZT from 28 weeks gestation until delivery. Since ART was only given to women who met the WHO clinical staging and those with a low CD4+ count, all HIV infected pregnant women not eligible for ART were given maternal AZT from 28 weeks of pregnancy or as soon as possible thereafter; single-dose NVP plus a 7 day tail of AZT and 3TC. Infants born to these women were given a one-week course of AZT (MoH, 2008).

Following new guidance from WHO on PMTCT of HIV and infant feeding in the context of HIV released in 2010, the government of Malawi, revised its PMTCT guidelines to align with the new WHO recommendations. However, considering the evidence that Malawi had gathered through implementation of previous PMTCT regimens and the high fertility rate of 6 children per woman's life time and mean breastfeeding period of 23 months (Schouten, 2013); Malawi opted to start lifelong ART for all HIV infected pregnant women and breastfeeding women regardless of CD4+ count or clinical stage also known as the option B+. This was thought to greatly improve the prevention of mother to child transmission of HIV and was believed to offer minimal differences in duration of ART over a woman's life time between option B and option B+ considering the high number of children women have in countries like Malawi (Schouten, 2013, MoH, 2011a). Option B+ was therefore a modification of the WHO recommendation which promoted lifelong ART for HIV infected women who needed it and short term ARV prophylaxis for prevention of MTCT of HIV during pregnancy, labour and delivery and breastfeeding for HIV infected women (WHO, 2010c) . In the current clinical management of HIV in children and adults guidelines, mothers already on ART continue the same ART regimen as pregnancy and breastfeeding is not regarded as a contraindication while HIV infected mothers not yet on ART or who stopped or interrupted, start lifelong TDF/3TC/EFV as soon as possible during labour or after delivery (MoH, 2014).

2.21 HIV/AIDS interventions in children

The population of HIV exposed children is constantly increasing following scale up of PMTCT interventions (UNAIDS, 2013a). Optimizing the survival of these children requires a careful assessment of the risks and benefits associated with interventions available for them. The World Health Organization promotes four components for effective prevention of mother to child transmission of HIV (WHO, 2010b). These include:

a) Primary prevention of HIV infection among women of child bearing age
b) Preventing unintended pregnancies among women living with HIV
c) Preventing HIV transmission from a woman living with HIV to her infant
d) Providing appropriate treatment, care and support to mothers living with HIV and their children and families

Prevention and management of HIV opportunistic infections remain critical components of care in HIV exposed children. ART significantly reduces severity of HIV disease (Patel, 2012) with significant rise in CD4+ cell percentage manifesting after 6 to 12 months of starting ART for all WHO clinical stages of HIV infection (Patel, 2012). Eighty-six per cent of new HIV infections in children in SSA have been prevented with the use of ART in pregnant women since 2005 (UNAIDS, 2013b). Before ART was widely available in resource limited settings, use of CPT in HIV infected children led to significant reductions in HIV opportunistic infections such as *Pneumocystis jiroveci* (formerly known as *Pneumocystis carinni pneumonia* (PCP) (WHO, 2006b). The ability of cotrimoxazole to reduce hospital admission rates as well as mortality in HIV infected children (Chintu, 2004), culminated in the recommendation by the World Health Organization that all HIV exposed infants born to mothers living with HIV should receive CPT starting at 4-6 weeks of age (or at first encounter with health care system) and continued until breastfeeding is stopped and HIV infection can be excluded (WHO, 2006b). However, this prophylaxis requires careful assessment of its benefits versus the detriments when given to HIV exposed children. Cotrimoxazole has been shown to be effective in reducing bacterial infections even in areas where there is a high background *in vitro* resistance to it (Chintu et al., 2004a). In addition, it potentially offers an effective and sustained malaria chemoprophylaxis, even in areas like Malawi, Uganda and others where resistance to sulphonamides may be high (van Oosterhout et al., 2005), and

significantly lowers incidence of malaria episodes, both parasitaemic and presumptive among both HIV exposed and HIV infected children (Graham, 2010). This could potentially impair the acquisition of natural immunity to malaria in infants and therefore abrupt cessation of cotrimoxazole use at 12 months after stopping breastfeeding in children who remain HIV negative could be associated with an increased risk of malaria in terms of frequency and severity in the following year.

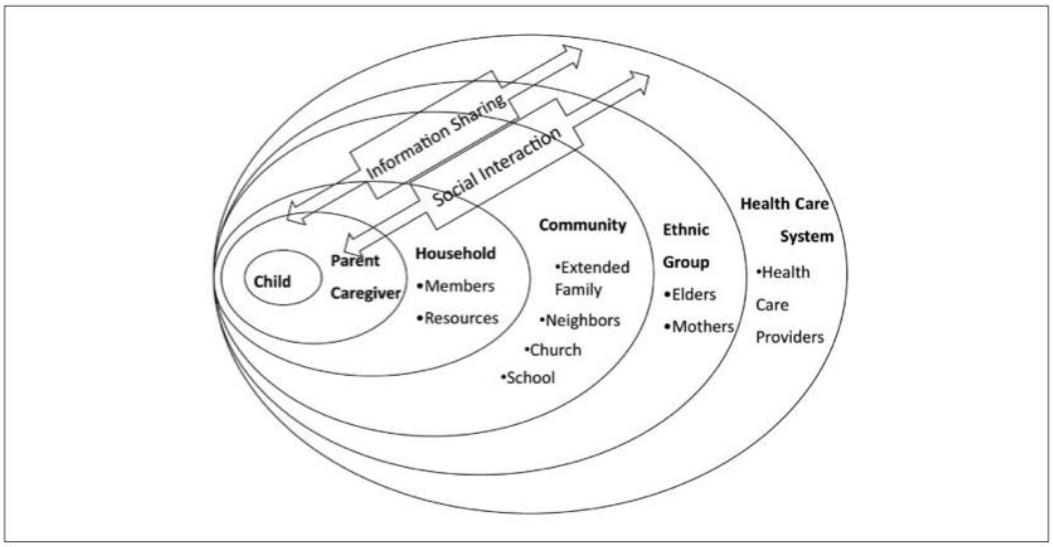
For these children, adherence to CPT is a major factor in ensuring optimal responses and is a significant predictor of survival. In HIV disease, ART adherence rates of 100% are required for optimal viral suppression. Surprisingly, adherence to ART in most African settings is believed to be lower than the 50% reported for developed countries (WHO, 2003a). A paucity of data on adherence in young children especially on CPT exists as most research has focused on adherence in adults. In these adults both personal and hospital related factors have demonstrated to play an important role in enhancing adherence to treatment. At its meeting in June 2001, the WHO adherence group recognized that adherence is a reflection of a certain type of behaviour towards taking an appropriate action and came up with a consensus definition of adherence as "the extent to which a person's behavior such as taking medications, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" (WHO, 2003a). Thus understanding factors that influence this adherence in HIV exposed children is key to identification of specific behaviour modifying interventions.

2.22 The complexity of long term treatments in young children

Little information is available about the extent of factors associated with long-term treatment in HIV disease in children. In terms of adherence to these treatments, a study of adults taking ART and cotrimoxazole for *pneumocystis carinni* pneumonia (PCP), showed that the majority of patients (79%) taking cotrimoxazole had detectable urinary cotrimoxazole (Eldred et al., 1998) which was used as an indicator of adherence. In most of these (≥80%), adherence was associated with presence of family and patients' beliefs of their ability to adhere to therapy (Eldred, 1998). In Africa where the majority of HIV infected and exposed children live, determinants of paediatric adherence to daily drug regimens have not been widely assessed

nor are the effects of the PMTCT programmes on family/household dynamics and how parents of HIV infected or exposed children cope with the situation. From a culturally grounded ecological theory perspective, Vreeman and others in Kenya described paediatric ART adherence to consist of relationships that exist between the child, parents, the care giver, household, community and the health care system that are connected by sharing of information as well as social interaction Figure 2.5. They explain that these interactions and any disintegration in the connections that exist between different entities may influence pediatric ART adherence (Vreeman, 2009). However, it is not known whether these theories could likewise explain paediatric CPT adherence as well as how the long term interventions for HIV exposed children would impact on the lives of guardians.

Figure 2.5: Culturally grounded ecological model of paediatric ART adherence



Source: Vreeman R.C. et al., Qualitative health research 19 (12) 1716-1729.

The culturally grounded ecological model is thought to close the gaps that exist with using the Health belief Model (HBM). Developed in the 1950s, the HBM was initially more concerned with the subjective state of the individual than with past experience (McCormick-Brown, 1999). Apart from the four main constructs which include: perceived seriousness, perceived susceptibility, perceived benefits and perceived barriers; the relationship between the health

professionals and the patient and availability of social support are believed to be important catalysts of behavior change (McCormick-Brown, 1999). The two theories (the culturally grounded ecological model and the HBM) therefore compliment each other to adequately explain people's behavior towards compliance to treatments.

In chronic non-HIV treatments in the United States, the process of adherence in children was more associated with family structure as well as relationship with healthcare providers. In addition religious beliefs and child related factors such as developmental stage and temperament were also some of the contextual issues to influence adherence (Landier, 2011). In order to determine the concepts that explain adherence to CPT in young children in our context, and unveil how the lives of mothers giving CPT to their young HIV exposed children evolve, there is need to understand the influence of interrelatedness of existing systems and how the women respond to them. A few studies in Malawi in HIV infected mothers, have mainly focused on the poor attendance to PMTCT clinics (Bwirire et al., 2008, Chinkonde et al., 2009). There has been no study that has properly described the lived experiences of mothers with HIV exposed children on CPT. There is need to understand cultural, social and personal environments that would determine how mothers of young children receiving daily CPT cope with the situation of caring for their children. Several authors have highlighted the lack of adequate information from health professionals as the reason for unpreparedness to provide care to sick relatives amongst most caregivers (Bucher, 2001). This puts the family members in an unfamiliar position with the type of care they must provide but also the amount of care that needs to be provided (Scherbring, 2002). There is evidence that caregivers receive very little information related to managing their tasks but also to emotional demands of caregiving (Scherbring, 2002). This is believed to originate from the inability of family caregivers to interact effectively with health professionals in the hospital setting making transition to home care a difficulty for many (Scherbring, 2002). In order to develop cost-effective plans of care and achieve positive client outcomes, health care providers need to communicate effectively with clients and caregivers. The evidence on household dynamics related to administering long term treatment to children in the communities in rural setting is scarce but would be helpful in formulating a theoretical perspective that may enhance understanding of factors that influence adherence and women's experience in general and form a basis for identifying appropriate interventions for complying to uptake of the services.

2.23 Factors associated with long-term medication adherence

Long-term medication adherence is influenced by self, family, community and forms of support available from them; healthcare system factors that take into consideration availability of resources and policies for accessing, making available and accepting medical services. There are also factors that are related to the intervention itself and patient characteristics (Murray, 2004). The suppositions that influence adherence to treatments in adults are suggested to be multi-faceted (**Table 2.9**) consisting of patient factors, healthcare factors as well as the type of treatment one is taking. It is not clear whether paediatric CPT adherence in HIV exposed children in influenced by the same factors.

Table 2.9: Factors associated with medication non-adherence

Patient factors	Type of Treatment	Healthcare factors	Social factors
• Actual or perceived side effects • Rejection of the diagnosis • Limited Understanding of the diagnosis • Loss of faith in medications • Poor memory • Lack of self-efficacy • Language or literacy barriers • Knowledge and understanding about the rationale of treatment • Beliefs	• Complex treatment regimen • Long duration of treatment • Previous treatment failure • Frequent changes in treatment • Lack of immediacy of beneficial effects • Side effects • Reduced access to medicines and/or medical support	• Health professionals lack of time • Lack of health professionals • Lack of continuity of care: changing providers • Lack of collaboration between health professionals • Lack of on-going communication • Poor medication distribution and costs	• Costs of transportation to the health facility • Low levels of patient education • Language barriers • Lack of effective social support

Source: Adapted from the national heart foundation of Australia (Aslan, 2011)

From a theoretical perspective, the Health Belief model, protection motivation theory, theories of reasoned action, self-efficacy, social cognitive and ecological theories of perception strongly contribute to the explanation of adherence to treatment (Biddle, 2000) (**Table 2.10**). The use of theories in explaining behaviour helps to describe the associations that occur between various factors and result in more effective behavior change interventions. Stepnowsky and others attributed the importance of using theories to guide research to the following reasons (Stepnowsky, 2013, Ritterband, 2009):

- help to describe (and explain) how behaviours change and symptoms improve through the use of behavioural change programs;
- guide program development and facilitate testing of the intervention;
- help to firmly link an intervention to a theoretical foundation;
- grounding adherence interventions in theory are important to help the literature build a foundation and grow over time

Table 2.10Table 2.10 is a summary of different theories related to adherence. Despite the wide existence of theoretical backgrounds to adherence to treatment presented, paucity of theories to explain adherence in young children exists.

Table 2.10: An Overview of behavioural theories related to adherence

Theory	Description
Social Cognitive theory (SCT)	The SCT is centered on four factors that influence an individual's behavior. In the first place the individual must be able to involve himself in a certain behavior and have self-belief that this involvement will result in a certain outcome i.e. adherence. Availability of social support from family, friends and medical staff are catalysts to behavior change that is enhanced because of accurate knowledge of the intervention (Bandura, 2004).
Cognitive behavioral therapy (CBT):	The CBT was formulated for post trauma patients whereby they use their traumatic experiences to adapt or influence the way they react to similar traumatic events in life. In CBT, an individual uses meanings, judgements, appraisals and assumptions he has encountered in life experience to influence his feelings and actions to respond to a particular life event such as adherence which thus deters or enhances the process of adaptation (Antonio). However if an individual encounters a new experience, he either assimilates it into the existing experience or adjusts the existing experience to fit the new experience. CBT has been shown to be effective for a wide range of situations including adherence to treatment (Resick, 1992).
Trans theoretical model (TTM):	The Trans theoretical Model (TTM) draws upon several other theories of behavior change. In this model, change is not instant but it occurs over time allowing the individual to progress through several stages (Lenio, 2014). Unlike other theories, in the TTM, the person relies on himself to make a decision to change behavior while in other theories influences of social support and biological factors play a major role (Lenio, 2014). The individual carries an appraisal of the situation in which he weighs the risks and benefits of the new behavior and decides whether to change behavior or maintain the present behavior depending on the outcome of the appraisal. In circumstances where the benefits outweigh the risks, behavior change takes place (Velicer, 1998, Scholl, 2002).
Health belief model (HBM):	The Health Belief Model (HBM) focuses on individual factors that may influence one's perceptions of either changing a behavior or not. In this model, for an individual to take a recommended action like adherence to treatment, he weighs benefits versus the barriers of taking a particular action. These may include physical, psychological or financial factors. For instance, a patient may realize the benefit of taking his treatment and adhering to it but may not be able to access it due to stock outs or other reasons or may not have adequate information about the medication instructions. In such a scenario, the patient may be motivated but since the medication is not available or there are no instructions on how to take the medications, the barriers outweigh the benefits and this may result in non-adherence to treatment. Moreover, with this model, individuals evaluate if they are susceptible to a particular threat and whether the threat is severe. In 1974, Rosenstock noted that motivation for an action results from a combination of perceived susceptibility and severity while the pathway for action is achieved by the comparison of perceived benefits to perceived barriers. Thus the likelihood that a positive action like adherence to treatment would be considered with increase in the strength of the perceptions of severity, susceptibility and benefits (which are mostly affected by demographics and previous experiences) and the weakness in perceptions of barriers (Rosenstock, 1974).

Table continued

Table 2.10 continued

Theory	Description
Health action process approach (HAPA):	According to Health action process approach (HAPA), for an individual to achieve a successful behavior change, goes through two phases: the pre-intentional motivational phase and the post-intentional volitional phase (Gaston, 2012). The first phase is primarily for forming an intention while the second phase is where the intention is translated into action. In a meta-analysis of 94 studies, Gollwitzer and his colleagues, individuals who are likely to follow through on their intentions are the ones who identify the context (how, when, where, with whom and for how long) in which they would perform the target behavior. Moreover, individuals are able to act on their intentions even in the presence of barriers if they pre-decide how to best avoid unwanted influences on behavior. The effects of action planning on behavior change are believed to be enhanced formulation of coping strategies for the anticipated barriers (Gollwitzer, 2006).
The ecological theory of perception	This is a general theory of perception and control of behavior that stresses the relation between the organism and its environment as well as the relation between perception and action such as adherence to medications. It focuses on the perception and control of behaviours that occur naturally and on aspects of the animal and the environment that determine the success or failure (CEHD, 2014). It largely aspires to describe, explain and predict perception and action by all animals and all situations at all ages (CEHD, 2014). This theory originates from the work of Eleanor Gibson, who emphasized direct perception via detection of higher-order stimulus variables, as opposed to reductionist, constructivist-representational account of perception (Braund, 2008).

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CHAPTER 3 : THE ROLE OF COTRIMOXAZOLE PROPHYLAXIS IN THE PREVENTION OF MALARIA IN SUB-SAHARAN AFRICAN CHILDREN: A SYSTEMATIC REVIEW AND META-ANALYSIS

3.1 Introduction

Globally, WHO estimates that there were about 207 million cases of malaria in 2012 and an estimated 627 000 deaths, with the great majority of malaria deaths occurring in sub-Saharan Africa in children under five years of age (WHO, 2013b). When these children are co-infected with HIV, they tend to have a higher malaria parasite density than HIV uninfected ones and HIV-1 infection is associated with severe and fatal malaria (Berkley, 2009). Independent of parasite density, both exposure to HIV-1 in children born to HIV-infected mothers and HIV infection are associated with severe malarial anemia during acute *P. falciparum* infection (Otieno, 2006). In HIV infected children, WHO recommends daily CPT until immune recovery is observed on antiretroviral therapy (ART) (WHO, 2006a). For HIV exposed children CPT is recommended from the age of four to six weeks until they stop breastfeeding and HIV infection is ruled out (WHO, 2006a).

Cotrimoxazole is an antimicrobial drug containing a fixed dose combination of sulfamethoxazole and trimethoprim. The combination of these drugs causes a synergistic bactericidal effect against a variety of bacterial infections and has also shown to be effective against protozoal infections (Wormser et al., 1982). Randomized clinical trials (RCTs), observational studies and economic analyses have shown that CPT is cost-effective in preventing PCP which accounts for a large proportion of AIDS diagnoses and deaths in infants with HIV infection and reduces morbidity and mortality among infants and children living with or exposed to HIV (Chintu et al., 2004b). Estimates of the effectiveness of CPT for preventing malaria, however, vary widely. For example, a clinical trial (Thera et al., 2005) showed that in Mali CPT had a 99.5% protective efficacy against episodes of clinical malaria and another RCT showed that in Uganda the reduction in the incidence of malaria was only 39% (Sandison et al., 2011). Nonetheless, the uptake of CPT by national programs has been slow meaning that CPT is being underutilized (Date et al., 2010, Hutchinson et al., 2011). A major concern with CPT is that its widespread use in high malaria transmission areas may favour cross-resistance to sulphadoxine-pyrimethamine (SP), a drug used for intermittent preventive therapy (IPT) for malaria in pregnant women (Sridaran et al., 2010). However, it

remains to be determined if the presence of antifolate resistant mutations affect the protective efficacy of CPT against malaria.

This systematic review of the literature and a meta-analysis explored the effect of CPT on malaria incidence and mortality in HIV positive, HIV exposed and non-HIV exposed children in different settings in sub-Saharan Africa. This chapter has recently been published in the Tropical Medicine and International Health journal (Mbeye, 2014).

3.2 Objectives

1. To assess the effectiveness of cotrimoxazole prophylaxis on prevention of malaria in children
2. To determine the effect of cotrimoxazole prophylaxis on all-cause mortality in children
3. To explore whether the effect of CPT on malaria prevention is affected by the prevalence of SP resistance.

3.3 Methods

3.3.1 Study design

A systematic review of relevant literature was conducted to assess the effect of cotrimoxazole on prevention of malaria and all-cause mortality in children but also whether the malaria preventive effect of CPT is affected by presence of SP resistance. The results of different studies were combined using meta-analysis in order to summarize and ascertain the effect of cotrimoxazole on the prevention of malaria in children in sub-Saharan Africa. Furthermore, a meta-regression analysis was used to explore the association between SP resistance and cotrimoxazole malaria preventive efficacy. As defined by the Cochrane collaboration, a systematic review attempts to collate all empirical evidence that fits pre-specified eligibility criteria to answer a specific research question. It uses explicit, systematic methods that are selected to minimize bias, thus providing reliable findings from which conclusions can be done and decisions made (Liberati, 2009). The same authors define meta-analysis as the “use

of statistical methods to summarize and combine the results of independent studies" (Liberati, 2009).

The methods for conducting the review and meta-analysis were specified apriori in a comprehensive protocol which was registered with the international prospective register of systematic reviews (PROSPERO) (Booth, 2013) The reporting of the review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines that consist of a 27-item checklist (Appendix 1) and a four-phase flow diagram essential for transparent reporting of a systematic review (Liberati et al., 2009).

3.3.2 Search strategy

In order to identify relevant articles for the subject, databases like PubMed and EMBASE were searched on May 29, 2013 looking for both RCTs and prospective cohort studies assessing the effect of CPT on the incidence of malaria and mortality in children aged 0-15 years in sub-Saharan Africa. Free text words and medical subject headings (Mesh) describing the age group, the intervention and the outcome were combined in PubMed. The detailed PubMed search, which was developed in collaboration with an expert librarian, is given in **Figure 3.1**. The PubMed search was adapted for EMBASE. Additionally, data on SP resistance was identified by contacting authors at the World Wide Antimalarial Resistance Network (WWMRN) in the USA. In terms of malaria transmission intensity, data was obtained from the published Malaria Atlas Project estimates for 2007 and 2010 of the *P. falciparum* parasite prevalence in children aged 2–10 years (PfPR2–10) (Hay et al., 2009, Gething et al., 2011) by matching by latitude and longitude, to the observational studies or trials that were included in the review. The PfPR2–10 data from 2007 were used for studies conducted between 2000 and 2008, and the 2010 estimates were used for the more recent studies.

Figure 3.1: The search strategy for PubMed

((((child OR children OR childhood OR infant* OR newborn* OR neonate* OR adolescen*)) AND (cotrimoxazole OR co-trimoxazole OR co trimoxazole OR trimethoprim-sulphamethoxazole OR trimethoprim sulphamethoxazole OR tmp-smx OR tmp smx OR bactrim)) AND (((malaria OR plasmodium OR plasmodium infection* OR paludis* OR malarial fever OR marsh fever)) AND ((((((therapy OR therapeut* OR treatment* OR pharmacotherap*)) OR (diagnosis OR diagnosed)) OR (epidemiol* OR preval* OR inciden*)) OR (mortalit* OR death* OR surviv* OR case fatalit*)) OR (prevention OR preventative OR preventive OR protect* OR prophyla* OR control OR controlled))))

OR

((("Malaria/diagnosis"[Mesh] OR "Malaria/drug therapy"[Mesh] OR "Malaria/epidemiology"[Mesh] OR "Malaria/mortality"[Mesh] OR "Malaria/prevention and control"[Mesh])) OR ("Mortality"[Mesh]))) AND (((((("Child"[Mesh]) OR "Child, Preschool"[Mesh]) OR "Infant"[Mesh]) OR "Infant, Newborn"[Mesh]) OR "Adolescent"[Mesh])) AND ("Trimethoprim-Sulfamethoxazole Combination"[Mesh])

3.3.3 Study Selection

All RCTs and cohort studies published between January 1990 and May 2013 that compared the incidence of malaria and/or all-cause mortality in children receiving and not receiving CPT were included. The exposure of interest for this review was Cotrimoxazole prophylaxis which was also the exposure investigated in the cohort study. However, in terms of HIV exposure, the review included HIV infected children in addition to HIV exposed but not infected children while only the latter were included in the cohort study in order to investigate rebound after stopping CPT. The inclusion of HIV infected and non HIV infected children helped to understand the effect of CPT across all children in SSA. No language restrictions were applied. Studies in adult populations aged 15 years and above and studies from regions other than sub-Saharan Africa were excluded. Two reviewers independently selected studies first based on titles and abstracts, and, in a second step, based on the full text of potentially eligible articles.

3.3.4 Data Extraction

A detailed data extraction form was developed (Appendix 2) and tested on four studies (2 RCTs and 2 Observational studies) and was refined accordingly before using it to extract data for this study. Two independent reviewers extracted data on the study design and setting, the characteristics of study populations, malaria incidence and mortality in children receiving CPT and control groups. In addition, data on the prevalence of sulfadoxine-pyrimethamine resistance–conferring point mutations in the dihydrofolate reductase (dhfr) and dihydropteroate synthase (dhps) genes was extracted. After extraction, the data between the two reviewers was compared. Disagreements were resolved by discussion between the two reviewers and a third reviewer.

3.3.5 Assessment of the risk of bias

For both RCTs and cohort studies, two reviewers independently examined each included study for risk of bias using a standard form. The form for RCTs included information on the sequence generation, allocation concealment, blinding (participants, personnel and outcome assessor), incomplete outcome data, selective outcome reporting and other sources of bias. The methodological components of the trials were assessed and classified as high, low or unclear risk of bias as recommended by the Cochrane collaboration (Higgins et al., 2011). Where differences arose, these were resolved by discussions with the third reviewer. For cohort studies, a checklist reproduced in Table 3.1 covered the selection of comparison groups, confounding, the assessment of exposures and outcomes, the completeness of follow-up and the reporting of outcomes was used to assess the risk of bias.

Table 3.1: Checklist for the assessment of the risk of bias in cohort studies

Domain	Description	Reviewer's assessment
Selection bias	***Were groups selected from the same underlying source population?***	Yes No Unclear
	Were the data collected for the purpose of this study?	Yes No Unclear
	Were the calendar periods of follow up the same in the two groups?	Yes No Unclear
	Was the comparability of groups assessed?	Yes No Unclear
	If yes describe the variables compared:	
	Potential confounders?	Yes No Unclear
	Outcome variables before intervention?	Yes No Unclear
Confounding	***Did the researchers describe how they decided which potential confounding domains should be considered?***	Yes No Unclear
	If yes describe the method used:	
	Did the authors control for confounding at the design stage?	Yes No Unclear
	If yes list on which domains participants were matched:	
	Did the researchers adjust for confounding at the analysis stage?	Yes No Unclear
	If yes, which method was used:	
	Stratification	Yes No Unclear
	Multivariable regression	Yes No Unclear
	Propensity scores (matching)	Yes No Unclear
	Propensity scores (multivariable regression)	Yes No Unclear
	Causal modelling (IPTW, g estimation)	Yes No Unclear
	What potential confounders were considered? Please provide list below:	
Information bias	***Were the defintions / approaches to assess exposures and outcomes the same in the comparison groups?***	Yes No Unclear
Loss to follow up	***Was follow-up near complete (>90%)?***	Yes No Unclear
Outcome reporting bias	***Did the study have a protocol pre-specifying the outcome?***	
	Malaria	Yes No Unclear
	Mortality	Yes No Unclear
	Was investigation of the effect of the intervention on the outcome a pre-specified objective of the primary study?	
	Malaria	Yes No Unclear
	Mortality	Yes No Unclear
Overall assessment	***What is the risk of bias in this study?***	High Low

3.3.6 Statistical Analysis

The primary outcome of interest was incidence of malaria and the secondary outcome was all-cause mortality. Inverse-variance random-effects meta-analysis was used to combine incidence rate ratios (IRR) for malaria and hazard ratios (HR) for mortality. Calculation of exact confidence intervals for the IRR and an estimate of the standard error of the IRR was obtained by dividing the difference of the log rate ratio and the upper confidence interval by 1.96. For cohort studies, results from analyses that maximally adjusted for potential confounders were used. Random effects meta-regression was used to assess the association between antifolate resistance and the effectiveness of CPT on malaria incidence. The markers used for resistance were the *dhps* A437G and the *dhps* K540E mutations. As *dhps* mutations have started to occur more recently and show a more geographically heterogeneous distribution than the major *dhfr* mutations (S108N, N51I and C59R), they were expected to have a stronger spatio-temporal correlation with SP efficacy. The *dhps* A437G mutation was used because the analysis included a study from West Africa, where the *dhps* K540E mutation is largely absent. For the two studies that did not report any resistance data, modeled data provided by the World Wide Antimalarial Resistance Network was used. The details of the data used in the model can be found on WWARN's Molecular Surveyor (http://www.wwarn.org/surveyor/) and http://www.drugresistancemaps.org (Flegg et al., 2013, Naidoo and Roper, 2013). Meta-regression was also used to examine whether the effectiveness of CPT depended on the study design (RCT or cohort study), the duration of the study, whether the children on CPT group were HIV-infected, or on the annualized parasite prevalence. All statistical analyses were performed using Stata version 12.1 (College Station, TX) and Comprehensive Meta-Analysis software.

3.4 Results

3.4.1 Study and participant characteristics

The searches of PubMed and EMBASE identified 500 publications. Screening of titles and abstracts resulted in 15 potentially eligible studies. Nine studies, including three RCTs and six observational studies met the inclusion criteria (Figure 3.2) (Sandison et al., 2011, Thera et al., 2005, Chintu et al., 2004b, Gasasira et al., 2010, Dow et al., 2012, Ezeamama et al., 2012, Desmonde et al., 2011, Kamya et al., 2007, Arinaitwe et al., 2012). Two reports (Kamya et al., 2007, Arinaitwe et al., 2012) were excluded because they were based on study populations already included in the analysis (Gasasira et al., 2010, Sandison et al., 2011). In total 1,692 HIV-

exposed, 2,800 HIV-uninfected and 1,486 HIV-infected children aged between six weeks (Dow et al.(Dow et al., 2012)) and 15 years (Thera et al.(Thera et al., 2005)) were included in the meta-analyses. The studies originated from six countries in sub-Saharan Africa: Uganda, Mali, Malawi, Tanzania, Zambia and Côte d'Ivoire. The number of children in each study ranged from 170 to 2,298 and the duration of follow-up ranged from 3 to 28 months. Transmission intensity at the time of the study was highest in the rural study site in Mali (Pfpr: 0·49) and in urban Côte d'Ivoire (0·68) and lowest in the urban sites in Tanzania and Zambia (0·07) (Table 3.2 and Table 3.3).

Figure 3.2: Flow Chart for identification of eligible studies

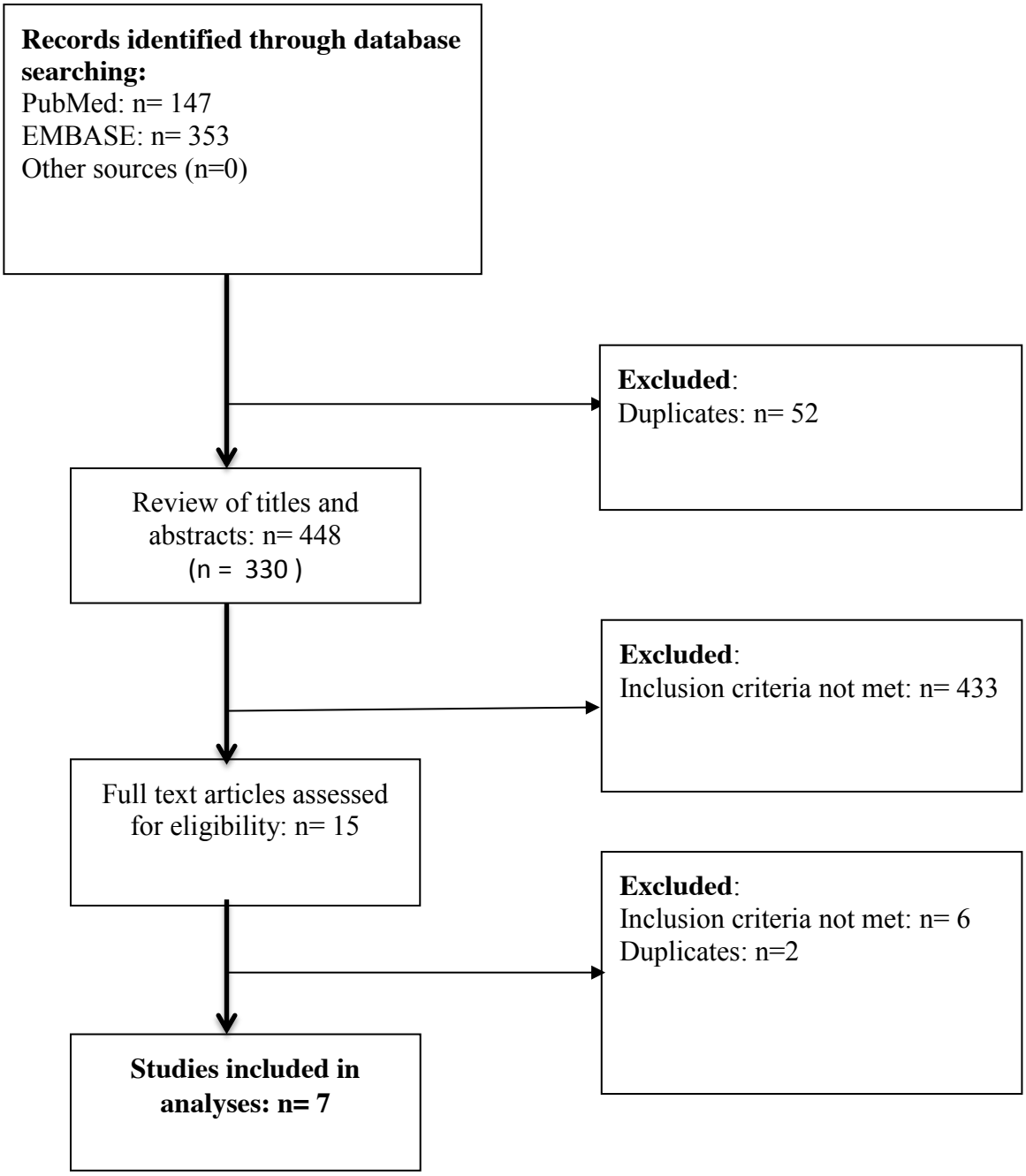


Table 3.2: Characteristics of studies and children included in the systematic review and meta-analysis of CPT and malaria incidence

Author (year)	Country (Setting)	Pfpr	Months of fup	Design	CPT regimen	Children in CPT group			Children in control group		
						No.	Age (years)	HIV status	No.	Age (years)	HIV status
Malaria incidence											
Thera (2005)	Mali (rural)	0.49	3	RCT	TMP 150 mg/m2 SMX 750 mg/m2 Thrice-weekly	160	10 (2.9)	Healthy children	80	10 (2.8)	Healthy children
Gasasira (2010)	Uganda (urban)	0.20	28	Cohort	Once-daily	292	6.0 (2.6)	HIV-infected	517	7.4 (2.7)	Healthy children
Sandison (2011)	Uganda (rural)	0.38	24	RCT	TMP 40-80 mg/kg SMX 200-400 mg/kg Once-daily	90	9.6 (8.3-12.4)	HIV_{ex}	80	10.0 (8.9-13.5)	HIV_{ex}
Dow (2012)	Malawi (urban)	0.34	6	Cohort	TMP 40mg/kg SMX 200mg/kg	1239	NR	HIV-exposed	283	NR	HIV-exposed
Ezeamama[1] (2012)	Tanzania (urban)	0.07	27	Cohort	NR	255	NR	HIV-infected & HIV_{ex}	2043	NR	HIV-uninfected

Abbreviations: NR: not reported; RCT: Randomized Controlled Trial, Pfpr: annualized parasite prevalence in children 2-10 years of age in X-survey

[1]The study by Ezeamama et al included 255 HIV infected and 2043 HIV exposed uninfected children. Cotrimoxazole prophylaxis was analysed as time-varying covariate, based on whether or not the mother reported giving cotrimoxazole to her child over the past month.

Table 3.3: Characteristics of studies and children included in the systematic review and meta-analysis of CPT and mortality

Author (year)	Country (Setting)	Pfpr	Months of fup	Design	CPT regimen	Children in CPT group			Children in control group		
						No.	Age (years)	HIV status	No.	Age (years)	HIV status
Chintu (2004)	Zambia (urban)	0.07	18.9	RCT	TMP 40-80 mg SMX 200-400 mg Once-daily	265	4.2 (2.8-8.3)	HIV-Infected	269	4.5 (2.1-8.2)	HIV-Infected
Desmonde (2011)	Cote d'Ivoire (urban)	0.68	12	Cohort	NR	271	NR	HIV-Infected	134	NR	HIV-Infected

Abbreviations: NR: not reported; RCT: Randomized Controlled Trial, Pfpr: annualized parasite prevalence in children 2-10 years of age in X-survey

Cotrimoxazole prophylaxis was analysed as time-varying covariate, based on whether or not the mother reported giving cotrimoxazole to her child over the past month.

3.4.2 Risk of bias

Overall, the studies included in this review were of high quality. All three RCTs reported adequate generation of random allocation sequences, whereas only Chintu *et al*. and Sandison *et al*. reported allocation concealment (Chintu et al., 2004b, Sandison et al., 2011). Chintu *et al*. used double blinding whereas the two others were open-label studies. The three trials adequately addressed incomplete outcome data: proportions of dropouts were low and outcome data was missing for less than 3% of children. There was no evidence of selective reporting in any of the studies. In each of the four observational studies included in this review, the CPT and non-CPT groups were selected from the same population and followed up for the same calendar period. The only exception was the study by Dow *et al*. in which the incidence of malaria was compared between HIV-exposed children before and after 2006, the year CPT guidelines were introduced in Malawi. All studies adjusted for potential confounders at the analysis stage; however, the variables included in the multivariable models differed across studies (**Table 3.4**). Finally, patient retention was over 80% in all the four cohort studies.

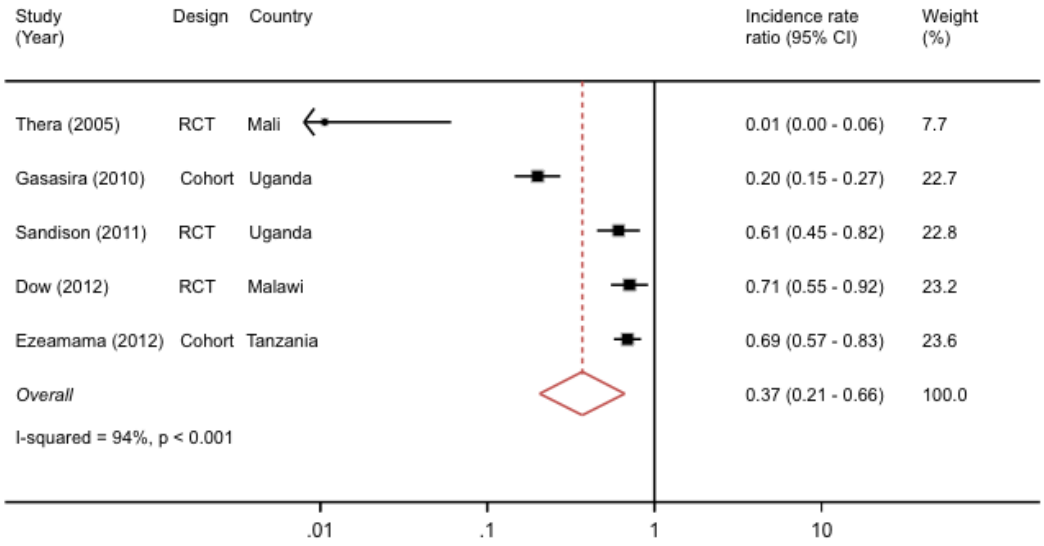
Table 3.4: Variables included in adjusted analyses from individual cohort studies

Study	Country	Variables adjusted for
Gasasira et al.	Uganda	Age Stratification by time periods
Dow et al.	Malawi	Age, rainy season, ART status, first pregnancy
Ezeamama et al.	Tanzania	Season Mother: Age, CD4, education, marital status, Socio-economic status, Bed-net use, history of neonatal mortality Child: CD4, sex, low birth-weight, CTX compliance, breastfeeding, intervention status
Desmonde et al.	Ivory Coast	Age, sex, CD4, PMTCT, mother dead, follow-up center

3.4.3 Malaria incidence

Five studies including 2,036 children on CPT and 3,003 not on CPT evaluated the association between CPT use and malaria incidence. Children on CPT were less likely to develop malaria episodes than those without prophylaxis (IRR 0·37, 95% CI 0·21, 0·66) but there was substantial between-study heterogeneity (I-squared=94%, p<0·001) (Figure 3.3). The RCT by Thera *et al* received little weight in the meta-analysis (8%). When it was excluded from analysis the efficacy of CPT decreased by 50% (IRR 0·50; 95% CI 0·30, 0·84) but between study heterogeneity remained similar (I-squared=94%, p<0·001). The four remaining studies included in this analysis all received weights between 23% and 24% Figure 3.3.

Figure 3.3: Meta-analysis of RCTs and cohort studies of the effect of CPT on the incidence of malaria in children



3.4.4 Prevalence of resistance mutations

Three studies analyzing the association between CPT and malaria incidence also reported on the prevalence of antifolate resistance mutations (**Table 3.5**) (Thera et al., 2005, Sandison et al., 2011, Gasasira et al., 2010). Gasasira et al. and Sandison et al. compared the presence of resistance mutations in children receiving and those not receiving CPT in moderate and high transmission areas in Uganda (Sandison et al., 2011, Gasasira et al.,

2010). The prevalence of the *dhfr*/*dhps* quintuple mutants, composed of the *dhfr* 51I, 59R, and 108N and *dhps* A437G and K540E mutations, was between 86% and 95% and there was no significant difference between comparison groups. Thera *et al*. reported on antifolate drug resistance in a moderate transmission rural area in Mali. In their study, 14% of the children had the triple *dhfr* mutants at baseline and the prevalence of this resistance pattern did not change during CPT. Double *dhps* mutants were not found (Thera et al., 2005).

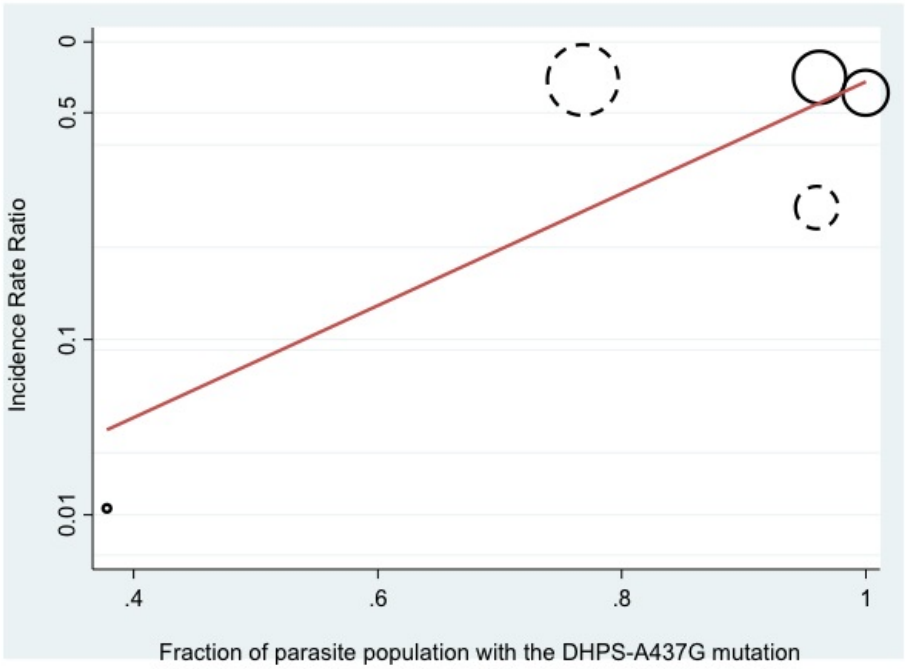
Table 3.5: Prevalence of antifolate resistance mutations in studies of the effect of CPT on malaria incidence

Study	**Thera et al.**	**Gasasira et al.**	**Sandison et al.**	**Dow et al.[1]**	**Ezeamama et al.[1]**
Country	Mali	Uganda	Uganda	Malawi	Tanzania
Study period	2000	2005-06	2007-08	2004-09	2004-08
DHPS gene mutations					
Gly-437 (437G)	38%	96%	100%	96%	77%
Glu-540 (540E)	0%	97%	100%	98%	71%

[1] Estimates for Dow *et al*. and Ezeamama *et al*. were obtained from modeled data provided by the World Wide Antimalarial Resistance Network. For details of the data used in the model see WWARN's Molecular Surveyor (http://www.wwarn.org/surveyor/) and http://www.drugresistancemaps.org.
DHPS: dihydropteroate synthase

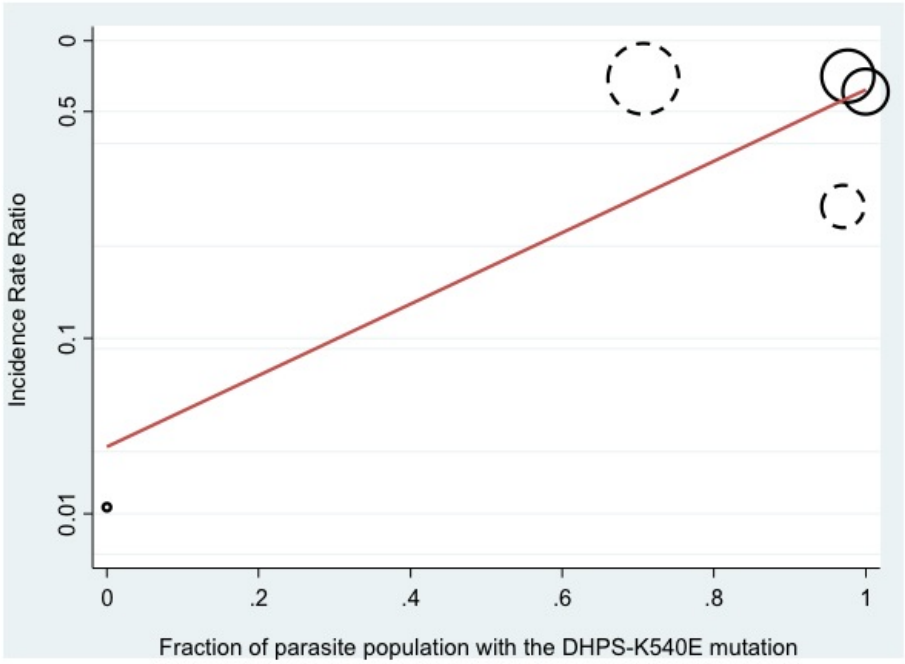
There was some evidence that the effectiveness of CPT decreased with increasing prevalence of the *dhps* A437G and *dhps* K540E resistance mutations as shown in Figure 3.4 and in Figure 3.4 respectively but this did not reach conventional levels of statistical significance (p=0·11 and p=0·09, respectively). There was little evidence that the reduction in malaria incidence was related to the study design (p=0·42), the duration of the study (p=0·42), whether the children on CPT were HIV-infected (p=0·75), or on the annualized parasite prevalence (p=0·35).

Figure 3.4: Results from meta-regression of the efficacy of CPT on malaria incidence in the presence of antifolate resistance mutations *dhps* A437G



Key: Dashed bubbles: Cohort studies; Solid bubbles: RCTs; red line: the regression line; The size of the circle is proportional to the inverse of the incidence rate ratio.

Figure 3.5: Results from meta-regression of the efficacy of CPT on malaria incidence in the presence of antifolate resistance mutations *dhps* K540E



Key: Dashed bubbles: Cohort studies; Solid bubbles: RCTs; red line: the regression line; The size of the circle is proportional to the inverse of the incidence rate ratio.

3.4.5 Mortality

One RCT from Zambia (Chintu et al) and one observational study from Cote d'Ivoire (Desmonde et al) reported on the association between CPT and all-cause mortality. 536 participants on CPT and 403 not on CPT were followed for 12-19 months. CPT reduced mortality by 43% (HR 0·57, 95% CI 0·43, 0·77) in the RCT. The crude estimate from the observational study was similar (HR 0·53, 95% CI 0·23, 1·25), however the protective effect of CPT disappeared after adjustment for age, sex and immunodeficiency status (HR 1·13, 95% CI 0·37, 3·43).

3.5 Discussion

This systematic review and meta-analysis of the effect of CPT on the incidence of malaria in children from four countries in sub-Saharan Africa has shown that CPT reduced malaria incidence by 63%. However, the number of studies included was small and the heterogeneity across them substantial. The protective efficacy of CPT seemed to depend on the population prevalence of resistance mutations in the parasite genes *Pfdhfr* and *Pfdhps* but remained important in areas with very high levels of antifolate resistance. The evidence on the role of CPT in reducing mortality among children was even poorer as only two studies could be included: an RCT from Zambia showing a statistically significant reduction of mortality by 43% with CPT and an observational study from Côte d'Ivoire reporting no difference between children receiving and not receiving CPT (Chintu, 2004, Desmonde, 2011).

Although the studies included in the meta-analysis of CPT and malaria were different in their design, study population and geographical settings, all showed a protective effect of CPT on the incidence of malaria. The reduction in malaria incidence was less (50% reduction) when the outlier (Thera et al.(Thera et al., 2005)) was excluded from the analysis, but the association between CPT and malaria incidence remained statistically significant. The study by Thera et al. (Thera et al., 2005) was the only one done in HIV-negative children, in whom the protective efficacy of CPT might be different than in HIV-infected children. Two cohort studies compared HIV-infected children on CPT with HIV-exposed or healthy children not on CPT (Gasasira et al., 2010, Ezeamama et al., 2012). HIV infection increases the risk of malaria and the protective effect of CPT might therefore have been underestimated in these studies. Interestingly, the impact of CPT on malaria incidence seemed to depend on the geographical area where the study was performed, possibly in relation with the prevalence of resistance mutations in *Pfdhfr* and *Pfdhps* genes. The meta-regression showed that there was a trend towards a higher protective efficacy of CPT on malaria in regions where the prevalence of the resistance mutation *dhps* A437G was lowest, but this was essentially driven by one study (Thera et al., 2005). Other factors including geographical differences in transmission intensity may also have played a role in generating this association. These results underline the paucity of data from regions other than East Africa and the lack of large studies in HIV-uninfected children. Of note, a study from Uganda showed that CPT was not associated with a higher

prevalence of resistance mutations in HIV-infected children and adults with *P. falciparum* parasitemia (Malamba et al., 2010).

This review confirms the substantial effect of CPT on malaria incidence and mortality in African children. Despite the limited evidence available, WHO has recommended CPT for all HIV-infected children for many years (WHO, 2006b). However, despite the low price and relative safety of the drug (Mermin et al., 2004), this preventive strategy has not been widely used for HIV-uninfected children. In a sub-study of the ARROW trial, in which children older than 3 years and on ART for longer than 96 weeks were randomized to continue or stop CPT, those who discontinued the drug were more likely to be hospitalized, including for malaria (Bwakura-Dangarembizi and al., 2013). The fact that the protective effect of CPT was most important in patients with high CD4+ cell counts supports the view that this might be a valid approach for malaria prevention in immune-competent children. However, there have been concerns that the widespread use of CPT would lead to an increase in antifolate resistance in sub-Saharan Africa (Lynen et al., 2007). These resistance mutations have shown to have an impact on the efficacy of sulfadoxine-pyrimethamine (Naidoo and Roper, 2013), which is currently the only drug recommended for intermittent preventive treatment (IPT) for malaria in pregnant women (Garner and Gulmezoglu, 2006, Menendez et al., 2007, Kayentao et al., 2013, ter Kuile et al., 2007). Only one study included in this meta-analysis assessed the prevalence of antifolate resistance mutations before and after the use of CPT and did not show an increase in the prevalence of these mutations over time (Thera et al., 2005), consistent with other CPT studies in HIV infected adults (Malamba et al., 2010, Malamba et al., 2006).

Although several publications have reviewed the evidence on the protective efficacy of CPT on malaria (Kamya et al., 2012, Manyando et al., 2013), this is the first report to include a meta-analysis and a thorough assessment of the risk of bias of both RCTs and observational studies. The most important limitation of this report is the low number of studies which could be included in the analyses. Only five studies were eligible for the meta-analysis assessing the effect of CPT on malaria incidence. As a consequence, it was not possible to conduct sub-group analyses to effectively assess sources of heterogeneity. Furthermore, as the publications originated from only four countries in Africa and also

that Asia was excluded, the results are not representative of the overall situation in sub-Saharan Africa and cannot be applied to other regions such as Asia. Moreover, Asia would not have added much to the review as pooling the findings would have been difficult considering the differences in malaria transmission epidemiology and co-existence of vivax with the hypnozoite stage (Price, 2009). The association between CPT and mortality was only evaluated in one RCT and one observational study. A meta-analysis was therefore not performed for this outcome. Finally, only one study evaluated the protective efficacy of CPT on malaria in HIV-uninfected children (Thera et al., 2005).

The omission of Septrin (an international brand name for cotrimoxazole) might only have had impact higher up in the flow chart but did not impact on the final number of studies included as all studies also mentioned the word cotrimoxazole. The many advantages of CPT prophylaxis in HIV-infected as well as those exposed to HIV but not infected (HIV exposed) justify its recommendation in routine clinical care. However, CPT is not widely prescribed to children who are HIV-negative, partly due to the lack of evidence and because, in contrast to HIV-infected children who are in regular medical care, the delivery of this treatment would not be straightforward in this population.

3.5.1 Summary of discussion

This study has described studies evaluating the effect of CPT on the incidence of malaria in children and has also provided a pooled estimate of its effect. Furthermore, it has shown how this effect is affected in the presence of antifolate resistance. In brief the study has shown that CPT reduces malaria incidence and mortality in children in sub-Saharan Africa but study designs, settings and results were heterogeneous. CPT appears to be beneficial to HIV-infected, HIV exposed as well as HIV uninfected children.

CHAPTER 4 : MALARIA REBOUND IN HIV EXPOSED CHILDREN AFTER STOPPING COTRIMOXAZOLE PROPHYLAXIS

4.1 Introduction

The population of HIV exposed children is constantly increasing following scale up of PMTCT interventions (UNAIDS, 2013a). Optimizing the survival of these children requires a careful assessment of the risks and benefits associated with interventions available for them. The use of CPT for the prevention of OIs (WHO, 2006b) has previously been associated with significant gains in reducing malaria and other morbidities in children in different African settings (Sandison, 2011, Mbeye, 2014, Kamya et al., 2007). However, it is not known whether the abrupt cessation of CPT at 12 months in HIV exposed children who remain negative may be associated with increase in the risk of malaria, all-cause morbidity, admissions and mortality. While a number of studies on the use of malaria chemoprophylaxis have reported an increase in the episodes of malaria and other morbidities in the year following termination of chemoprophylaxis (Greenwood et al., 1995, Menendez et al., 1997, O'Meara et al.), a pooled analysis of six trials using SP for IPTi was not able to show rebound effects (Aponte, 2009). This study aimed at comparing the incidence of uncomplicated and severe malaria; all-cause sick visits, all-cause hospital admissions and all-cause mortality between HIV exposed and non-HIV exposed children during CPT and after it was stopped.

4.2 Methods

The overall aim of this study was to investigate malaria rebound after stopping cotrimoxazole prophylaxis in HIV exposed children. This chapter therefore, presents an overview of the methods that were used and furthermore, it describes the study location, detailed study procedures, data management, statistical methods used and ethical processes. Thereafter, the study findings are presented followed by a discussion of the findings.

4.2.1 Study location

This study was carried out in Zomba district in the Southern region of Malawi (Figure 4.2). With a population of approximately 15 million (Group, 2013), Malawi, a landlocked country stretches over 118,484 square kilometres sharing borders with Tanzania, Mozambique and Zambia. For administrative purposes, the country is divided into 28 administrative districts headed by a District Commissioner (DC) (MLGRD, 2013). Within

the districts there are Traditional Authorities (TAs) comprising of specific village groups (MLGRD, 2013). The TAs play important roles in maintaining public peace, assisting in general administration and reinforcing any lawful directions of the DC (Cammack, 2009). The Malawi economy is agro-based with Agriculture accounting for 30.2% of the Gross Domestic Product (GDP) per capita of 360 USD in 2012 (Bank, 2013).

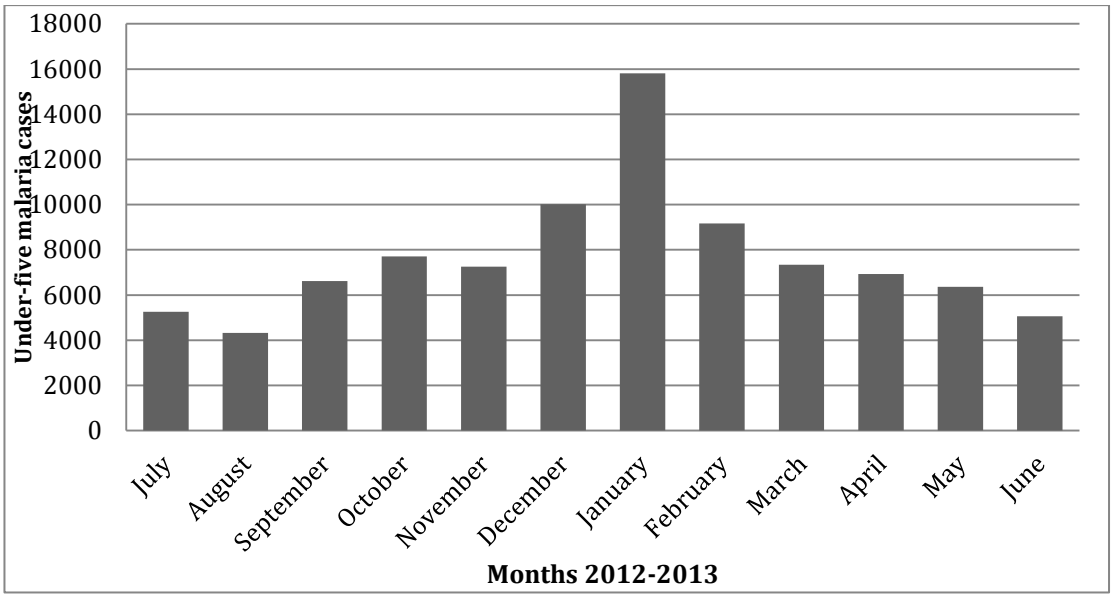
With a mean annual rainfall varying between 635mm and 3,050mm for a rainy season lasting from November to April, Malawi experiences a sub-tropical climate which is more prominent in the lowland areas of the southern region with temperatures reaching as high as 39 degrees Celsius. Most of the northern region is relatively cooler with temperatures averaging between 20 and 27 degrees Celsius due to the highland areas common in this region (Services., 2007).

4.2.1.1 Zomba District Profile

Zomba district has a population of 670,533 and has a mixture of a peri-urban and rural population (Council., 2010). Its topography varies from hilly areas of Zomba plateau with an altitude of 2,085 metres above sea level to broad, flat plains of Lake Chilwa lying at an altitude of 627 metres below sea level (MLGRD, 2013). The district extends into the Phalombe plains where the prevalence of HIV among antenatal attendees was estimated to be 27% in 2007 (NAC, 2008). It also extends to Domasi area where HIV prevalence in 2007 was 34% among antenatal attendees, second highest after Thyolo district located in the same region. Between 2012 and 2013 the district registered a monthly average of 155 HIV infected pregnant women and 198 new HIV exposed newborns (MoH, 2013a). Health care services are provided by the Ministry of Health (MoH), private organizations and non-governmental organizations (UN-HABITAT, 2011). There is an active PMTCT program at the hospital, run in conjunction with Dignitas International, a medical humanitarian organization dedicated to improving access to treatment and quality of care for people with HIV/AIDS and related diseases (Dignitas., 2013). Malaria in this region is endemic with high rates of severe malaria observed in hospital. Most of these admissions are in younger children aged between 1 and 4 years (Kazembe et al., 2006). The risk of dying in hospital for these younger children is higher compared to older children aged between ten and fourteen years (Kazembe, 2006). Spatial modelling of hospital paediatric data showed that malaria-specific mortality was higher in areas further from the district

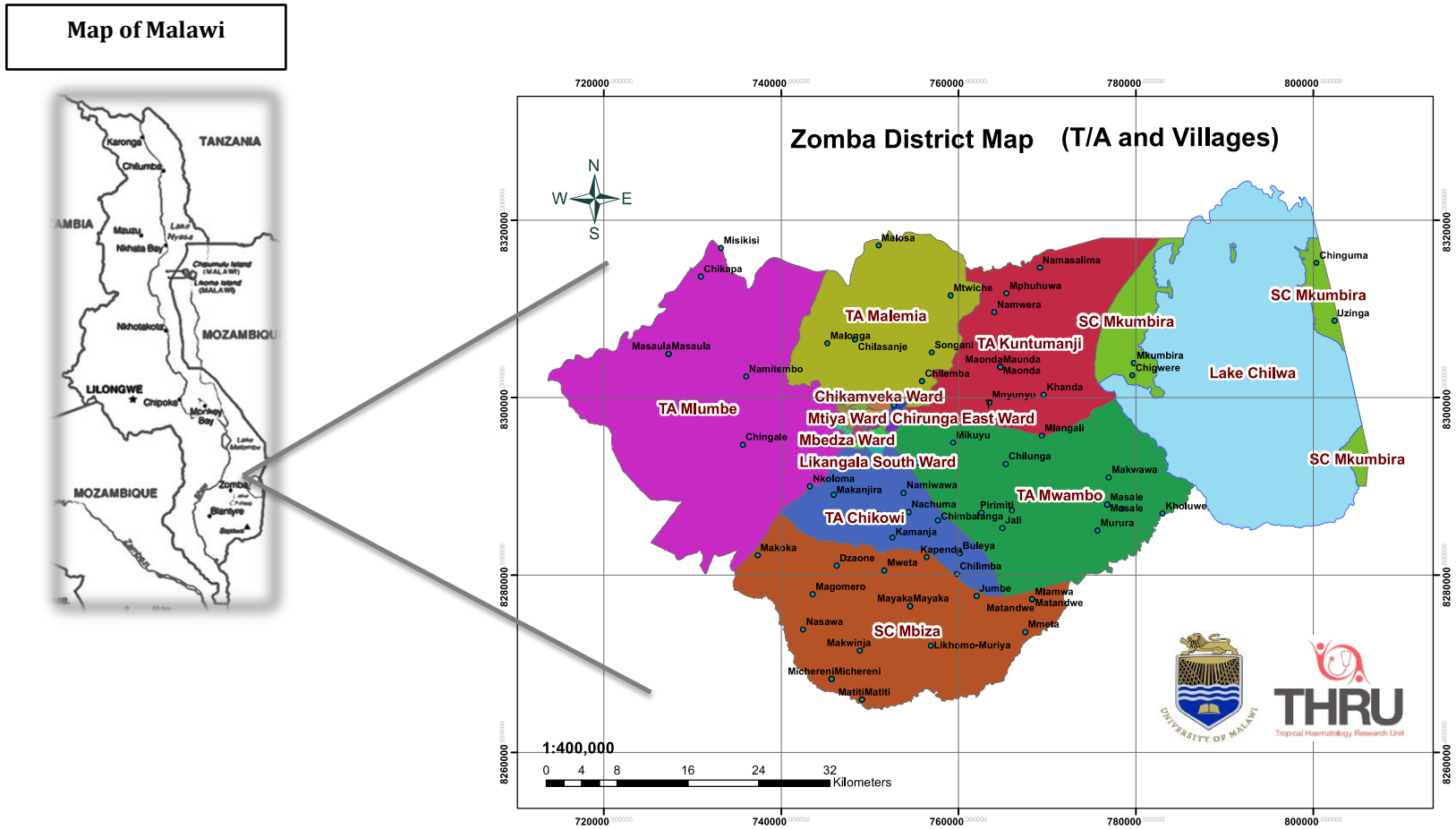
hospital and higher during the wet season (Kazembe, 2006). In terms of malaria control interventions, ITN coverage rose from 5.9% in 2000 to 30.3% in 2010 among people of all ages (NSO, 2011) largely due to free ITN distribution campaigns by the MoH (Okiro, 2013). More recent raw data by the HMIS at district level indicates a monthly average of 7,655 malaria cases among under-five children in the district (MoH, 2013b) with more cases attended to in the month of January (Figure 4.1).

Figure 4.1: Under-five malaria cases in Zomba district 2012-2013



This site was chosen because of the malaria and HIV disease epidemiology, the already set-up infrastructure and the proximity to College of Medicine, Blantyre where storage of study samples and all procurement of study supplies was done. The study catchment area covered the whole district comprising of 9 TAs, 4 sub TAs and 1,561 villages (Figure 4.2). Some parts in TA Mlumbe were deliberately excluded because of high terrain during the rainy season. Since study follow-ups were home-based, it would have been impossible to reach participants by a motorbike during the rainy season.

Figure 4.2: Map of Zomba district showing TAs and villages



4.2.2 Study Design

A prospective cohort study was used to follow up two groups of children. One group was HIV exposed and received daily CPT from 6 weeks until the age of 14 months, while the other group was non-HIV exposed not on CPT. Since the groups were not assigned to specific forms of treatment or exposures by the study, as would have been the case in experimental studies (i.e. trials), a cohort design was used where 'exposure' (i.e. CPT use) was based on routine care and the HIV status of the mother rather than by the study (Bookwala, 2011). Experimental studies have previously been used to investigate the effect of CPT on malaria. For example, in one randomized clinical trial in Uganda, HIV exposed children who remained HIV negative after stopping CPT, were randomized to either continue on CPT or on placebo for 2 years (Sandison, 2011). This could have been the only way to achieve a nearly ideal comparison group, as randomizing them at the beginning would have had ethical implications. However, with such a design it would have meant extending the period of CPT in half of the children, which has practical and ethical limitations because of the unclear risk/benefit of the additional year of CPT. Another trial in Lilongwe used the same group of HIV exposed children, by taking their time before starting CPT as the unexposed period and time after they started CPT as exposed period. In studies like these where comparisons of outcomes for the two different periods are made for the same population (Dow, 2012); the difference in the time of outcome assessments makes it impossible to separate temporal changes in disease occurrence due to changes that may arise like the availability of malaria control interventions such as ITNs, IRS and other forms of prevention at specific time points. In the same pursuant of trying to achieve an ideal comparison group, some studies have randomized children of unknown HIV status into CPT and placebo (Gasasira et al.). As much as the groups are similar in some baseline characteristics with this type of randomization, unequal distribution of HIV infection between the groups would modify the effect of CPT, plus the ethics of withholding an intervention that is national strategy in some of the children can be debated.

4.2.2.1 Description of exposure

The exposure under investigation in the present study is CPT that was administered according to body weight once every day (Figure 4.3) in HIV exposed children from the age of six weeks until the age of 14 months when they were stopped from breastfeeding and tested HIV negative with both antibody and HIV PCR tests as part of PMTCT

interventions (WHO, 2010f). The exposure was not assigned to study participants by the investigator, but as part of normal PMTCT interventions, HIV exposed children receive this prophylaxis to prevent bacterial infections (WHO, 2006b). Naturally, this created an exposed group. Under normal circumstances, the ideal comparison group would have been HIV exposed children who are not on CPT. However, this was not possible due to ethical implications since it is a WHO recommendation to put all children in this category on CPT (WHO, 2006b). The only available comparison group therefore, was non-HIV exposed children born from HIV negative women. The selection of an age and residence matched comparison group in this study took into consideration environmental as well as personal attributes that may influence malaria in these children.

Figure 4.3: The dosing schedule for Cotrimoxazole prophylaxis in children

Trimethoprim/sulfamethoxazole CTX/SMZ, Cotrimoxazole, Septrim®, Bactrim®		
Age	**Suspension** 40 mg TMP/200 mg SMZ per 5ml	**Single-Strength Tablet** 80 mg TMP/400 mg SMZ
< 6 months	2.5 ml daily	1/4 tab daily
6 months-5 years	5 ml daily	1/2 tab daily
6-14 years	10 ml daily	1 tab daily
> 14 years		2 single-strength or one double-strength tab daily

Updated June 2006

Source: UNICEF and WHO, 2009 (UNICEF, 2009)

4.2.2.2 Study Procedures

Baseline assessment of PMTCT services in selected districts

Before the study protocol was written, a formative research was carried out in selected hospitals located closer to the College of Medicine in Blantyre to determine the status of PMTCT services and understand the target problem (Power, 2004, Ulin, 2005). This assessment included questions on breastfeeding practices of HIV infected women with HIV exposed but not infected children, uptake of PMTCT interventions, availability of Early Infant Diagnosis (EID) services and availability and nature of follow up mechanisms. In addition to interviews, hospital records and registers were checked to

determine the magnitude of the situation. The hospitals that were assessed were the Queen Elizabeth Central Hospital (QECH) in Blantyre, Thyolo District Hospital, Chiradzulu District Hospital and Zomba Central Hospital. The findings of this assessment are not part of this report but were used to understand the context as well as guide in the study design and selection of the study site.

Study preparatory procedures

After the study team was assembled, a five-day study specific training for all study staff was conducted. The staff included a Study Coordinator who was a Clinical Officer responsible for coordinating clinic activities and examining study participants when they reported for scheduled and unscheduled clinic visits; two research nurses who worked closely with the PhD student in data collection as well as collection of blood samples; Laboratory Technicians who assisted with reading of malaria slides and three Research Assistants/field workers who assisted the PhD student in conducting home visits and dispensing of cotrimoxazole at home. During the training, the review of the study protocol with emphasis on methods for data collection and orientation on Standard Operating Procedures (SOPs) were covered. Two days were dedicated to practical experience of using Personal Digital Assistants (PDAs) during dry runs. This was repeated several times until everyone had mastered the processes. PDAs are electronic devices that were used for capturing data for the study as described in section 4.2.2.3. The dry runs presented opportunities to clarify the intent of the study and its procedures. Some areas that required revision were identified and revisions were made before conducting the 'wet run' a few days before starting the study at the study site. The 'wet run' involved taking a child with characteristics similar to study participants through all study procedures in order to validate the study tools as well as procedures.

The management team of ZCH provided a clinic space with a reception area, a laboratory, a counselling room where informed consenting process took place, an examination room which was dedicated for performing physical examinations and collection of blood specimens, and a data room where the touch screen computers and the server were housed (Figure 4.4).

Figure 4.4: Study clinic at Zomba Central Hospital

District Sensitization meetings

Several steps were taken in order to seek permission to conduct the study in the district and create awareness about the study among the community members. Immediately after permission to carry out the study at the site was granted by the Director of ZCH, successive awareness meetings with all government departments including the police, city assembly, district assembly, district health office and non-governmental organizations took place. District-wide meetings with Traditional Authorities and Group Village Headmen (GVH) followed. Separate meetings to brief all hospital departments at the study site about the study and how each department was going to be involved preceded the start of the study. Health Surveillance Assistants (HSAs) and Community Advisory Board (CAB) members with assistance from field project staff supplemented GVH sensitizations to reach out to everyone in the study catchment area. The CAB comprised of lay people in the community who were trained on the study protocol using layman's language for them to understand study aims and procedures. With this information, CAB members were able to create awareness about the study but also alert study staff on any arising

misconceptions about the study from the communities. In addition, they helped to dispel rumours and clarify any misunderstandings related to the study in the community.

Participant Screening

Pre-screening procedures

Every morning, the study team carried out health education talks at the under-five and antenatal clinics to sensitize the women about the study. Other talks were done in support groups of HIV infected women and PMTCT clinics. The study also targeted the labour and post-natal wards with messages about the study. All women interested to join were asked to present to the study clinic for detailed explanation about the study and undergo screening procedures.

Screening procedures

A checklist to assess the eligibility of study participants was administered to all guardians of the children that presented to the study clinic. For the HIV exposed group, between 0-2 months old HIV PCR negative children that were breastfeeding but also receiving CPT were eligible for the study. Study staff ascertained that their guardians were willing to comply to study protocols and planning to reside in the study catchment area for the duration of the study before the informed consent was obtained. Children with serious illnesses or severe malnutrition were treated during the screening process and allowed to take part in the study once they recovered. For the non-HIV exposed children, the same eligibility criteria were applied except that they were not supposed to be on CPT. The study staff verified that the mother was HIV negative by checking her health passport book records. Records for all participants who were screened were recorded in the screening log. The log also indicated whether the participant was enrolled in to the study or not with reasons for non-enrolment clearly specified.

Recruitment of study participants

HIV exposed children were recruited from the hospital (labour ward, post-natal ward, PMTCT or under-five clinic) and were escorted to their homes by the study staff where an age and residence-matched, non-HIV exposed child was identified. This offered the opportunity to take a detailed location map for further follow ups which were mostly home-based but also allowed ease of follow up for participants who missed their scheduled clinic follow up visits. In the community, the non-HIV exposed child was randomly selected by spinning a Coke bottle and following the direction it pointed for at least 100 metres, the first child who resided along this path meeting the inclusion and

exclusion criteria was selected. If there were no children after 100 metres, the bottle was spun again until a child was found. The aim of the careful selection of non-HIV exposed children was to provide a non-biased comparison sample of the population from which the HIV exposed children came from (Rothman, 2012). No information was divulged on the sero-status of mothers participating in the study during selection of study participants. In addition, the study was generally called "the malaria study" in the community to avoid suspicions that some of study participants were HIV infected. These meticulous procedures were aimed at ensuring that the non-HIV exposed children also had the background prevailing risk factors for diseases especially malaria and patient attributes. By selecting non-HIV exposed children from same residency as HIV exposed children they had comparable environmental malaria attributes. Information on both child and household characteristics was collected (Appendix 3). Details for participants enrolled in to the study were recorded in the enrollment log.

Follow up of study Participants

After recruitment, each participant was followed until the age of 14 months in the first part (year 1) of the study. During this time, home-based, two-monthly study visits were conducted. Participants were told to report to the study clinic when they were sick and at visit 6 which occurred when the children reached 12 months of age. Additionally, since HIV exposed children received CPT during this time, they were requested to come to the study clinic again at visit 7 for HIV PCR results and stopping of CPT (Appendix 5). For non-HIV exposed children, visit 7 was done at home. The same 2-monthly visit schedules were done for the second part (year 2) of the study until children reached 24 months of age.

Follow up procedures during cotrimoxazole prophylaxis

Between recruitment and the time the children stopped CPT at visit 7 which occurred when children were 14 months of age, both groups were primarily followed in their homes every two months by study staff except when they were sick and when they had specific clinic visit schedules. This was done in order to avoid introducing bias in their health seeking behaviour (Rothman, 2012). For both clinic and community-based study visits, the study staff noted whether the child was alive or dead or suffered any illness since the last visit which was unreported; collected information on malaria control measures and checked anthropometric measurements including height, weight and Mid-Upper-Arm Circumference (MUAC). Vital signs like temperature, respiratory rate and pulse rate were

only checked during scheduled clinic visits (Appendices 4,5,6) as well as unscheduled clinic sick visits (Appendix 7). All participants were advised to come to the study clinic for any sickness. CPT and adherence counselling were provided to HIV exposed children accordingly during these visits.

Clinic based follow up visits

During the follow up period, there were scheduled and unscheduled clinic visits for both groups of children. Apart from the study enrollment visit, both groups of children were requested to come to the study clinic at visit 12 which was the last study visit as explained later. However, HIV exposed children were requested to come at visit 6 when they were 12 months old for HIV testing and stopping of breastfeeding but also at visit 7 when they were 14 months old for HIV PCR results and stopping of CPT. Information collected at these visits was similar to that collected during community follow-up visits. During the unscheduled sick child visits to the study clinic, a detailed past history of illness since the child was last seen by study staff was collected including any information on hospital admissions and laboratory investigations (Appendix 8). All the information given was crosschecked with the information recorded in their health passport books. In addition, study participants underwent a full physical examination. During all sick visits a dry blood sample was collected on a filter paper for genotyping for recrudescent malaria infections in addition to a blood sample for Haemoglobin (Hb) and malaria smear. Children with parasitaemia were managed according to standard MoH guidelines. For a diagnosis of uncomplicated malaria, children were prescribed artemether lumefantrine (AL). Severe cases were given parenteral quinine and admitted to the hospitals children's ward for observation and further medical care. For other diagnoses, treatment was also given according to guidelines. HIV exposed children continued to take CPT unless medically contraindicated. Although rarely, any identified period during which CPT was not taken was duly recorded on the CPT adherence questionnaire.

Home-based follow up visits

During home visits, study participants who were not found in their homes were visited again within the following three days. Compliance to treatment including cotrimoxazole is generally difficult to measure. Random spot checks and unannounced pill counts were done in a subset of the study population to monitor adherence. Additionally, scheduled face-to-face CPT adherence interviews to identify any missing doses of cotrimoxazole and

reasons for missing the drug were conducted every four months with all guardians of HIV exposed participants.

Although this was not a clinical trial, drug safety was assessed. CPT may be associated commonly with rash, fever, anaemia and more rarely with severe hepatitis and Stevens Johnson syndrome in children (Hamel et al., 2008).

Follow up procedures after stopping cotrimoxazole prophylaxis

This section describes methods of follow up of both HIV exposed and non HIV exposed children in their second year of follow up when the HIV exposed group stopped taking daily CPT.

For HIV exposed children, present WHO guidelines on HIV and infant feeding strongly recommend that breastfeeding should be stopped when the child is 12 months old (WHO, 2009b). Previous guidelines recommended that women stop breastfeeding when children were 6 months old, however many studies have shown that this is associated with an increased child mortality versus the potential benefit of reducing the risk of HIV transmission through breast milk (Taha, 2011). Therefore, in this study, when HIV exposed children reached 12 months of age, they were advised to stop breastfeeding. Cabergoline, a drug that stops lactation within a day on average was given (Melis, 1988, Rains, 1995) as a directly observed single dose of 2 mgs to facilitate cessation of lactation. This drug is presently being used in PMTCT programs and is found to be highly acceptable and effective (Buhendwa, 2008). At this point, the child was reviewed in the study clinic and a filter sample of blood was taken as per PMTCT guidelines for HIV PCR testing. Since it takes around 6 weeks to have results for HIV PCR available, HIV exposed children were asked to report back to the study clinic for results and termination of CPT upon the nature of results. During this visit if the child remained HIV negative, CPT was stopped after HIV PCR results 8 weeks later (at the age of 14 months). This was properly documented. However, if the child sero-converted, CPT continued and was referred to the HIV clinic to start taking antiretroviral therapy and was informed to continue to report to the study clinic when sick for medical review and the study staff continued to follow up the child every two months until they were 24 months old.

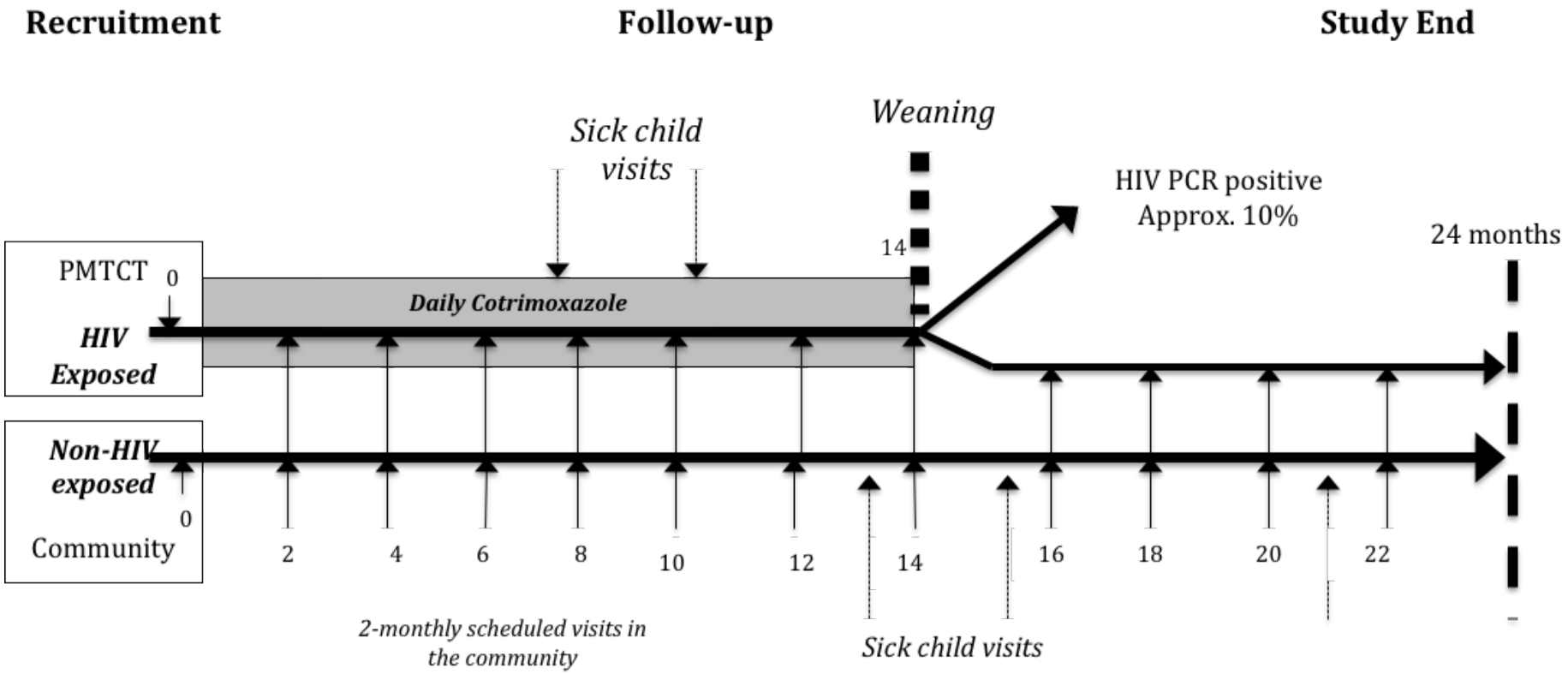
The HIV exposed children who remained HIV PCR negative after stopping cotrimoxazole prophylaxis and the non-HIV exposed children were followed up until they were 24

months old. They were visited in their homes every 2-months according to the same follow-up schedule in the first year except that CPT adherence interviews were not conducted. Both HIV exposed and non-HIV exposed children were requested to come to the clinic whenever they were sick. During these sick-child visits, these children underwent a full physical examination. A blood sample for Hb and malaria assessment plus a filter paper blood sample for genotyping for recrudescent malaria infections were collected. For every illness including malaria, children were managed according to standard MoH guidelines. **Figure 4.5** is a presentation of study participant flow. A follow-up period of around 10 months post-intervention was selected to observe for rebound malaria effect as most previous studies investigating this effect followed participants for a similar duration of time (Greenwood et al., 1995, Menendez et al., 1997). However, the data available for analysis has a wide variation between study participants on the period observed after CPT as the study is still on going. There are some participants who completed the 10 months of follow up while others did not. At visit 12, the last visit in the study, all participants were asked to come to the study clinic for final evaluation. During this visit, information on their past and current medical history was collected; the study clinician performed a full physical examination on all participants and blood samples for malaria parasites, anaemia and Dry Blood Sample were collected (Appendix 9).

Study termination procedures

At 24 months of age, all children were terminated from the study. In order to avoid separation anxiety, discussions on upcoming end of the study were initiated at visit 9 when children were 18 months of age and continued until termination date. Study termination procedures included one-on-one discussion to review the purpose of the study and the reasons for coming to an end. In addition, guardians of HIV exposed children were counselled on prevention of any infections among the children.

Figure 4.5: Participant flow during study follow-up



Laboratory procedures

In the study, blood specimens were collected at first study visit (enrollment visit), visit 12 (last study visit) and each sick child visit to the study clinic (Appendix 8). The blood specimen was collected to check for presence of malaria parasites, haemoglobin levels and future studies for genotyping and malaria recrudescence analysis. Passive surveillance was the main method of assessing malaria and anaemia to minimize discomfort, added suffering and risk associated with drawing of blood samples for research use, hence blood drawing was only limited to sick children and few scheduled visits so that it was in concert with procedures for medical care (Howie, 2011). Blood samples at the first visit in the study (enrollment visit) were collected to serve as baseline indicators. All Laboratory technicians working on the samples were unaware of the group the study participants belonged to in order to minimize chances of misclassifying the outcomes.

Assessment of malaria

For a malaria diagnosis to be made, an assessment algorithm and definitions in Table 4.3 was followed. The history of fever within 24 hours, temperature of ≥37.5 degrees Celsius and positive malaria smear by either microscopy or malaria rapid testing constituted a malaria diagnosis. Both thick and thin smears were collected from each participant at enrolment; every sick visit and at the last study visit.

Malaria microscopy: This study used malaria microscopy as the main method for malaria diagnosis. Thick blood smears were collected and examined for *P. falciparum* asexual parasites. A thick smear was collected by finger prick and placed on a clean microscopy slide. It was then allowed to dry in the open air for up to 20 minutes. The slides were stained using Field stain and read under light microscopy by a first reader who was an experienced Laboratory Technician (Lab Tech). Another Lab Tech independently read these slides again in order to achieve precision. A third reader read all slides with discrepant results, defined as malaria slide positive for first reader and malaria slide negative for the second reader for the same study participant. Independent readers performed quality control checks by reading randomly selected slides. A thick smear was considered negative if 100 high-power microscopic fields revealed no parasites. For positive smears, malaria parasites were counted against 200 leucocytes.

Malaria Rapid Diagnostic Tests (mRDT): The Ministry of Health introduced use of mRDTs for malaria diagnosis in 2012. This method was adopted by all health facilities in Malawi including the present study. Paracheck *Pf* Rapid Test was used in this study as a supplementary test to malaria microscopy from 2013. This test detects *P. falciparum* histidine rich protein II in whole blood and is accurate in isolating *P. falciparum* infection. As per the manufacturer's specifications, a drop of blood collected by finger prick was placed in a square shaped hole. This was followed by putting two drops of buffer solution in another hole that was round shaped. A positive result for *P. falciparum* was confirmed when both the control and the test line were present. However, if only the control line was present, the test was negative. In circumstances where the control line did not appear, the results were considered invalid and the test was done again. The results were read between 15 and 20 minutes from the time the buffer was added.

Anaemia assessment

Haemoglobin was checked on every study participant at enrolment, visit 12 (last study visit) and each sick visit. The test was done using a Hemocue® analyser (HemoCue AB, Ängelholm, Sweden). The child was pricked and after wiping the first drop of blood, the next capillary blood was collected using the microcuvettes which were then cleaned on the sides to wipe off any blood overflows before inserting them into the HemoCue machine. Each day, the machines were validated for control using the manufacturer supplied quality control kits. All quality control readings were recorded in a logbook.

Dry Blood Sample:

A DBS sample was collected at visit 1 (enrollment); every sick visit and visit 12 (when children were 24 months old) on a filter paper for genotyping for malaria recrudescence analysis in future.

HIV testing

HIV testing in this study was done by Zomba Central Hospital as part of PMTCT services at the hospital. Children were tested using HIV PCR at 6 weeks of age to determine their HIV status. These tests were repeated when the children reached 12 months of age using both HIV PCR and rapid testing with Unigold. The HIV PCR was performed at the Queen Elizabeth Central Hospital in Blantyre. This delayed the turn-around-time for the results which were a determinant for either stopping or continuing with CPT. As such HIV exposed children reported back to the study clinic eight weeks later for a decision on CPT to be made. Study participants who sero-converted at this visit were referred to the HIV

clinic to start antiretroviral therapy but continued to be attended to in the study clinic when they got sick until the end of the study.

Other blood tests

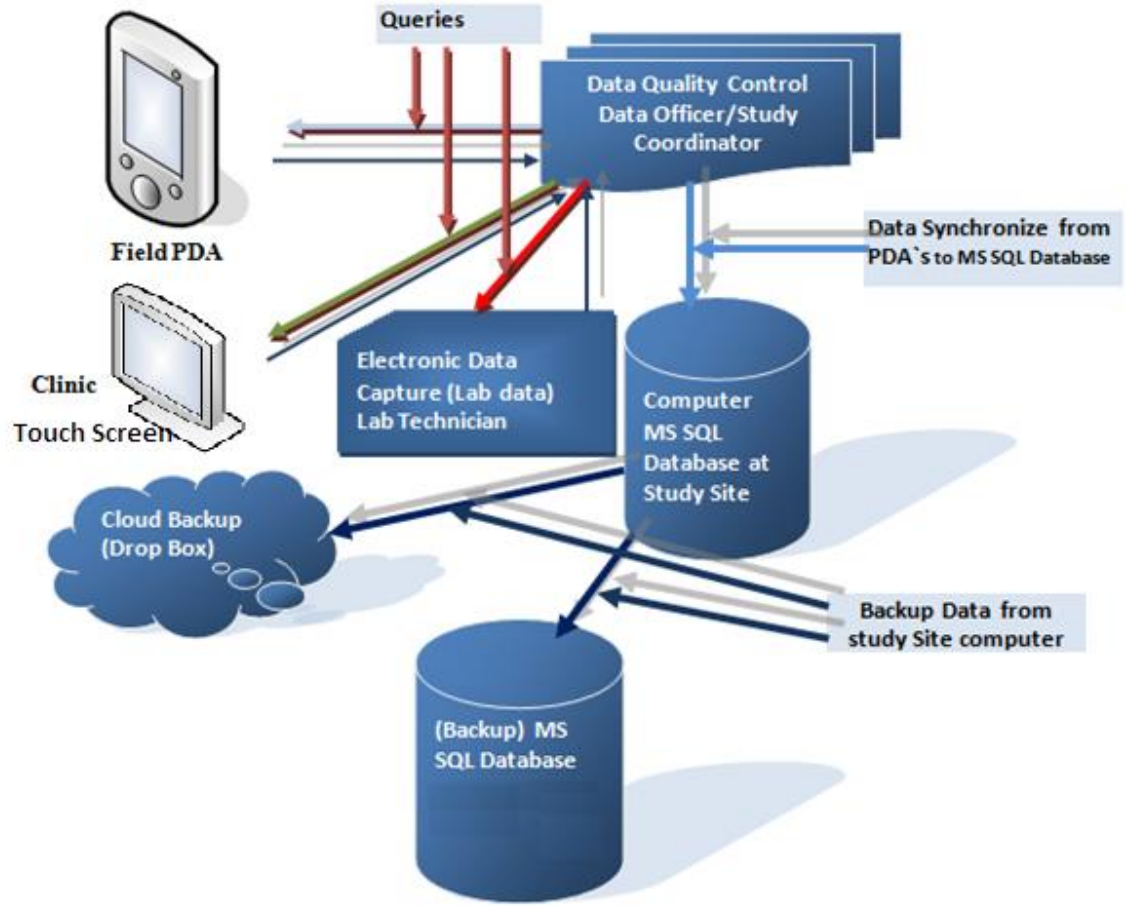
During a sick child visit, extra tests as needed for medical management of the patient were performed. These included a full blood count and differentials, peripheral blood smear for red cell morphology and others. No tests were performed during community follow-up visits. DBS and already read malaria slides were transferred to the College of Medicine laboratory in Blantyre for storage.

4.2.2.3 Data Management

Data Collection

A team comprising of four Research Assistants (RAs) or field staff followed up study participants in their homes on their scheduled visit dates. Data was collected electronically using PDAs (Figure 4.6). These PDAs were pre-programmed and uploaded with electronic Case Report Forms (eCRFs) using Visual CE programming software. The eCRFs had crosschecks for verification, validation rules and complied with Good Clinical Practice (GCP). After returning from the field, the PDAs were connected to the desktop allowing data to be directly uploaded into the database. The desktop was installed with MS SQL server that automatically backed up the data. In addition to administering visit-specific eCRFs (Appendix 4), RAs also checked weight, height and Mid-Upper arm circumference.

Figure 4.6: Electronic data management flow



For both scheduled and unscheduled clinic based study visits, data was collected using source documents in form of hard copies as well as visit-specific eCRFs uploaded on the clinic-based touch screen computers. The source documents were used to record a narrative of participants' aim of the visit, vital signs and physical examination findings and the action that was taken. The touch screens were directly linked with the database allowing instant synchronization of the data in the main database. The same mechanisms were utilized in the Laboratory (Lab) where the data for test results were directly entered into the lab database on the desktop computer installed in the Lab and this was instantly synchronized with the main database. At every point validation rules acted as check points for any errors.

Data Cleaning

Each participant record was checked for any missing values, typing errors, correct coding and variable naming. Missing values were corrected by verifying with source documents. Appropriate corrections were made following GCP rules. Team meetings were done every Friday to discuss study implementation issues and ways of improvement. In addition, both planned and impromptu meetings were done with the PhD supervisor on any matters requiring urgent attention.

4.2.2.4 Statistical Methods and Data analysis

Sample size

The sample size calculations were performed using the PASS 2008® software, version 08.0.7 (Hintze, 2008). For the primary objective of rebound malaria effect during the post-intervention period, the expected incidence of malaria in the non-HIV exposed children was assumed to be 0.8 per child per year. It was also assumed that during the entire two-year period of study 10% of children were going to die, 10% lost to follow-up and among the HIV exposed children 15% would become HIV PCR positive and continue on CPT. Thus if 500 children were recruited in each group 400 non-HIV exposed children and 340 HIV-exposed children who would not seroconvert were expected to complete the study (i.e. 740 children). It was anticipated that there was going to be over-dispersion, i.e. that the variability in the number of episodes of malaria for each child would exceed the mean. There were no data available on which to base an estimate for this. It was therefore anticipated that the parameter lied between 1 and 3. The study incidence rate ratio (IRR) detectable with 80% and 90% power for sample of 740 children and various values of the dispersion parameter is indicated in Table 4.1 Table 4.1 below.

Table 4.1: Values of dispersion parameter for the Incidence Rate Ratio

Power	IRR detectable for dispersion of:		
	1.0	2.0	3.0
80%	1.26	1.38	1.47
90%	1.30	1.44	1.56

It was anticipated that the incidence rate ratio for HIV exposed children post CPT compared with non-HIV exposed children would be at least 1.8, however the minimum IRR of interest was considered 1.5. The study thus had at least 80% power to detect an

IRR of 1.5 provided the dispersion parameter did not exceed 3. For the secondary objective of comparing the incidence of uncomplicated and severe malaria in HIV exposed children while **taking** CPT with non-HIV exposed children it was anticipated that the incidence in the non-HIV exposed children would be at least 1.0 per child per year and that the IRR would be reduced to 0.2 or less. If the dispersion parameter was 3 and 400 children in each group completed this phase of the study there was 90% power to detect an IRR of 0.63, and more than 99% power to detect an IRR of 0.2.

Methods for data analysis

Descriptive statistics were used to calculate frequencies and summaries of covariables. Chi-square test was used to detect any differences in categorical baseline characteristics between HIV exposed (HIV_{ex}) [‡] group and non-HIV Exposed (HIV_{un}) [§] group. The Fischer's exact test was used for contingency tables where the expected values in any of the cells were ≤5. In order to detect the differences in normally distributed continuous baseline characteristics, a two-sample t-test was used. Time at risk was calculated by subtracting the date of starting CPT from the date of exit from the study when children either completed study follow-ups at 24 months of age or when they withdrew from participation because of relocation or withdrawal of consent and when they died or sero-converted. In cases where the exit date due to loss to follow up was not known, the last date of contact was considered as the exit date. The association between baseline characteristics and incidence of uncomplicated malaria was explored using multiple negative binomial regression analysis that also accounted for over-dispersed incidents. Other regression methods were also explored for the multivariate modelling, including Poisson regression, zero inflated negative binomial and Poisson regression models, and use of either cluster robust standard errors or random effect models. The random effect was included in the models to capture the correlation between malaria incidence measurements in year 1 and year 2 in each participant. The negative binomial regression models showed the best fit based on the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) (Table 4.2). The general form of the models that were fitted to the data was $\text{Log}(\mu) = \text{Constant} + \beta_1\text{group} + \beta_2\ \text{year} + \beta_3\ \text{group*year}$. The natural logarithm of follow up time was used as an offset because study participants had different follow up time.

[‡] HIVex is short form for HIV exposed children/group used in the this section, the results and discussion sections
[§] HIVun is a short form for non-HIV exposed children/group used in theis section, results and discussion sections

Multiple regression models were constructed to adjust for covariates that were associated with the outcome of interest. Covariables with clinical and statistical significance of $p \leq 0.20$ associated with the primary outcome were selected and tested for collinearity using the spearmans correlation test before inclusion into the initial full model. If collinearity was detected, defined as a correlation of 0.6 and above, one of the two variables was selected for inclusion in the full model to prevent the model from becoming unstable. The adjusted and unadjusted incidence rate ratios (IRRs) and corresponding 95% confidence intervals for the effect of group (HIV_{ex} vs. HIV_{un}) and year (year 1 vs. year 2) on the incidence of uncomplicated malaria, all-cause sick visits, all-cause and malaria specific hospital admissions (severe malaria) and all-cause mortality were calculated by performing separate multiple regression analyses using models specified in Table 4.2Table 4.2. As CPT was typically discontinued at the age of 14 months, the variable year was defined as year1: aged ≤14 months and year2: >14 months. The effect of confounding was explored using the impact of removing each covariable on the main effect estimate and the corresponding precision of the estimate (i.e. the width of the confidence intervals). If removal from the model of one covariable changed the effect estimate by >5% or negatively affected its precision, it was regarded as a potential confounder and kept in the final model. This process was repeated with each covariable until the final model remained with all the potential confounders. Kappa statistic was used to calculate agreement of malaria microscopy results between the two malaria slide readers. All analyses were performed using STATA version 13 statistical software.

Table 4.2: Model selection for multivariate analysis

Outcome	**Model**			
	Negative binomial with cluster robust standard errors		**Random effects negative binomial (beta random effects)**	
	AIC	**BIC**	**AIC**	**BIC**
Uncomplicated malaria	**2371.549**	**2396.537**	2386.412	2416. 397
All-cause morbidity	3845. 106	3976.932	**3717.229**	**3872.596**
Severe malaria	1041.726	1167.353	**1037.828**	**1163. 455**
All cause hospital admissions	1042.543	1174.369	**1014. 181**	**1141.3**
All-cause mortality	**Log-binomial regression**			

Abbreviations: AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion

4.2.3 Ethical Considerations

4.2.3.1 Ethical Approvals

The study protocol was jointly reviewed and approved by the College of Medicine Research and Ethics Committee (COMREC) (Appendix 10) and the Ethics Committee at the Liverpool School of Tropical Medicine in Liverpool, United Kingdom (Appendix 11). Permission to carry out the study at the study site was sought from the Hospital Director of Zomba Central Hospital. Any amendments to the initial protocol were submitted to the two ethical committees for approval. Every year, annual progress reports on the study were submitted to both committees.

4.2.3.2 Informed Consent

The Informed Consenting process took place in a private room at the study clinic. Since the study involved young children, the process was done with their guardians. An informed consent form (Appendix 12 and 13), which was translated into Chichewa, the common local language in the district (Council., 2010), was read out to the guardian in the same language. At the end, the guardian was asked a few questions from the informed consent form to check the level of comprehension. Throughout the process, the guardian was encouraged to ask questions on areas she/he did not understand. If the person understood and voluntarily agreed to participate in the study, she/he was asked to sign the informed consent form. For illiterate guardians, the process was done in the presence of a witness who was a third person not associated with the study and the signing was done by

thumb printing. The original signed Informed Consent form was kept at the study clinic while the copy was given to the guardian for further reading at home. Guardians were encouraged to come back for clarification if they had any more questions. The Informed Consenting log was used to record the consenting process indicating time the process started and ended, whether participant was literate or not and whether the witness was available. Details of a person obtaining the informed consent from the guardian were also included.

4.2.3.3 Confidentiality

Each study participant was assigned a study number for identification. These numbers were generated by an independent person and were consecutively assigned to participants as they were enrolled. There were no unique differences in the numbering between HIV exposed and non-HIV exposed children. This was done deliberately in order not to influence the way study staff measured the study outcomes, as the two groups were different. Participants' names and any personal identifying information only appeared on the source documents which were always kept under lock and key. Access to these was limited to authorised study staff. No personal identifying information was used in data analysis as well as in any reports. Also, the two groups had separate informed consent forms. This was done so that HIV negative mothers (mothers of non-HIV exposed children) were not made aware of the HIV status of their counterparts (mothers of HIV exposed children) in order to minimise stigma and discrimination since they were residing in the same locations.

4.2.3.4 Benefits

Study participants had access to some medical services at the study clinic throughout their participation in the study. A dedicated Clinical Officer attended to study participants at every scheduled visit and at any point they presented to the clinic sick. The participants were closely monitored for any side effects related to cotrimoxazole prophylaxis. For all scheduled study visits, transport costs were reimbursed appropriately.

4.2.4 Study Outcomes

The primary outcome was the incidence of uncomplicated malaria defined as either confirmed uncomplicated malaria or uncomplicated malaria. Secondary outcomes were all-cause sick child visits, malaria specific hospital admission (severe malaria), all-cause hospital admissions and all-cause mortality as described in Table 4.3.

Table 4.3: Definitions of study outcomes and how they were assessed

Outcome	Definition	Mode of assessment
Incidence of uncomplicated malaria	**1. Confirmed uncomplicated malaria** • History of fever within 24hours or no history of fever within previous 24 hours • Febrile on examination or patient not febrile • Presence of parasitaemia with mRDT or microscopy **2. Clinical malaria** • History of fever within 24hours or no information on the symptoms • Febrile on examination or not febrile • No confirmation or presence of parasitaemia with mRDT or microscopy • Malaria treatment was given	Use of lab methods such as microscopy and malaria rapid diagnostic tests Use of health records from the child's health passport Use of medical history and clinical findings upon physical examination
Incidence of all-cause sick-child visits	Any visit by the study participant to the study clinic with any type of sickness including malaria	Use of health records from the child's health passport Clinical and physical examination findings
Malaria specific hospital admission	A hospital admission due to a confirmed diagnosis of malaria	Health records from child's health passport and source documents Past admission history
All-cause hospital admission	A hospital admission due to any other cause except malaria	Health records from child's health passport and source documents Past admission history
All-cause mortality	Death from any other causes	Use of verbal autopsy

4.3 Results

A total of 1000 children were enrolled during a 14-month period between June 2011 and August 2012. This was 2 months longer than the initial target of 12 months because of national fuel shortages that struck the country during the study period. Of the 1000 children, 500 were HIV exposed (HIV_{ex}) and 500 were non-HIV exposed (HIV_{un}). By the end of the follow-up period, five (1.0 %) HIV_{ex} children had sero-converted by their first birthday. Of the 10 participants who had withdrawn due to either permanent relocation outside the study catchment area or withdrawal of informed consent from the study, half (50%) were HIV exposed. There were a total of 18 deaths in the HIV exposed group and 8 in the non-HIV exposed group during the study follow up period. The total observation time was 9,515 months for year 1 and 4,751 months for year 2. In comparison, HIV_{ex} children were followed up for a longer period (mean follow up of 10 months) than HIV_{un} children (mean follow up of 5 months) with a mean difference of 5 month, (95% CI 1.6, 11.2), $p<0.001$. Year 1 covered the period from 6 weeks when the HIV_{ex} children started taking CPT to 14 months when they stopped taking CPT after HIV PCR results. In the second year, participants were followed from 15 to 24 months of age which henceforth is referred to as their 'year-2' in the analysis.

4.3.1 Baseline characteristics of study participants

The two groups were comparable in terms of sex, ethnicity, religion and other health and social demographic characteristics as presented in Table 4.4 and Table 4.5. Significant differences were observed in their age, anthropometric measurements, and parent characteristics such as age of mother, education of mother and job of both mother and father. On average, HIV_{un} children were slightly older at enrollment than HIV_{ex} children with a mean difference in age of 3.5 days (95% CI 0.52, 6.39), p=0.02 reflecting that the HIV_{ex} child was recruited first followed by an HIV_{un} child in the community. This could explain the significant differences observed in anthropometric measurements (weight, length and MUAC) between the two groups. Although about 8% of the children in both groups reported to have had suffered a febrile illness in the four weeks preceding the study, a small proportion (0.4%) had parasitaemia at enrollment (Table 4.4). The level of education of the mother was lower in the HIV_{ex} group (P=0.03), but the education levels of the fathers were comparable. In terms of household characteristics, HIV_{ex} children had slightly less access to safe drinking water but both groups were comparable in terms of the type of dwelling roofs of their houses (p=0.5) (Table 4.5).

Table 4.4: Child socio-demographic and health characteristics

Characteristic	HIV Exposed (HIV_{ex}) (N=500)	Non-HIV Exposed (HIV_{un}) (N=500)	P-Value
Child socio-demographic characteristics			
Age in days, mean (SD)[1]	35.9 (26.1)	39.4 (26.1)	0.021
Sex, n (%) Males Females	 249 (49.8)) 251 (50.2)	 223 (44.6) 277 (55.4)	0.1
Ethnic Background, n (%) Yao Others	 157 (31.4) 343 (68.6)	 165 (33.0) 335 (67.0)	0.701
Religion, n (%) Moslem Christians	 75 (15.0) 425 (85.0)	 90 (18.0) 410 (82.0)	0.208
Child Health Characteristics			
Weight at enrolment, kg[2] (SD)	4.4 (1.16)	4.7 (1.19)	<0.001
Length at enrolment, median, cm (range)	52 (36-66)	53 (38-69)	<0.001
MUAC[3], median cm (range)	11 (8-17)	12 (8-17)	<0.001
Temperature, mean degrees Celsius (SD)	36.8 (0.54)	36.7 (0.59)	0.002
Haemoglobin level, mean g/dl (SD)	12.6 (3.0)	12.7 (2.80)	0.24
Malaria parasitaemia, n (%)	2 (0.4)	0 (0.00)	0.157
Febrile illness in the preceding 4 weeks, n (%)	41 (8.2)	42 (8.3)	0.909
Admission to hospital in the preceding 4 weeks, n (%)	21 (4.2)	13 (2.6)	0.163
Current malaria treatment, n (%)	0.0 (0.0)	0.0 (0.0)	-

[1]SD: Standard Deviation; [2]Kg: Kilograms; [3]cms: centimetres; [4]MUAC: Mid Upper Arm Circumference

Table 4.5: Parents' and Household characteristics

Characteristic	HIV_{ex} Group	HIV_{un} Group	P Value
Age of mother, median years (range)	29 (17-45)	23 (15-45)	<0.001
Marital Status, n (%)			
In marriage	437 (87.4)	450 (90.0)	0.122
Not in marriage	63 (12.6)	50 (10.0)	
Education: Mother, n (%)			
No formal education	50 (10.0)	28 (5.6)	0.031
Primary Education	273 (54.6)	281 (56.2)	
Secondary Education	166 (33.2)	183 (36.6)	
Tertiary Education	11 (2.2)	8 (1.6)	
Education: Father, n (%)			
No formal Education	14 (2.8)	16 (3.2)	0.355
Primary Education	180 (36.0)	162 (32.4)	
Secondary Education	228 (45.6)	256 (51.2)	
Tertiary Education	47 (9.4)	46 (9.2)	
Unknown	31 (6.2)	20 (4.0)	
Job Mother, n (%)			
Employed	60 (12.0)	33 (6.6)	0.003
Not employed	440 (88.0)	467 (93.4)	
Job Father, n (%)			
Employed	361 (72.2)	333 (66.6)	0.01
Not employed	112 (22.4)	149 (29.8)	
Unknown	27 (5.4)	18 (3.6)	
Use of Electricity, n (%)			
Uses electricity	136 (27.2)	115 (23.0)	0.057
Does not use electricity	364 (72.8)	385 (77.0)	
Main water Source, n (%)			
Tap	290 (58.0)	297 (59.4)	<0.001
Borehole	155 (31.0)	180 (36)	
Stream	4 (0.8)	3 (0.6)	
Unprotected well	51 (10.2)	20 (4.0)	
Dwelling roof type, n (%)			
Iron sheets	310 (62.0)	303 (60.6)	0.524
Grass thatched	187 (37.4)	196 (39.2)	
Roof tiles	3 (0.6)	1 (0.2)	

4.3.2 Use of ITNs and other malaria control measures at baseline

No differences were observed in the number of mosquito nets in use in the home (net ownership) between the HIV_{ex} and the HIV_{un} group. Four hundred and thirty-one (431) households reported owning ≥1 mosquito net in each group. In terms of having the child sleep under a mosquito net the previous night, more HIV_{un} children slept under any mosquito net (96.1% HIV_{un} vs. 90.2% HIV_{ex}, p =0.001) compared to having a child sleep under an ITN which was used by a slightly higher proportion of HIV_{ex} children (88.7% HIV_{ex} vs. 86.9% HIV_{un}, p =0.006). The most common reason for not using an ITN was forgetfulness. At household level, use of indoor residual spraying, mosquito repellent practices and traditional medications were uncommon in households for both HIV_{ex} and HIV_{un} children (Table 4.6).

Table 4.6: Use of Insecticide Treated Nets for malaria prevention

Malaria control indices	HIV_{ex}	HIV_{un}	Overall	P-value
Number of mosquito in use in the home, n (%)				
0	69 (13.8)	69 (13.8)	138 (13.8)	0.47
>1	431 (86.2)	431 (86.2)	862 (86.2)	
Are nets treated, n (%)				
Yes	391 (90.7)	395 (91.7)	786 (81.2)	0.631
No	40 (9.3)	36 (8.4)	76 (8.8)	
Child slept under a net the previous night, n (%)				
Yes	388 (90.2)	413 (96.1)	801(93.1)	0.001
No	42 (9.8)	17 (4.0)	59(6.9)	
Child slept under an ITN the previous night, n (%)				
Yes	345(88.7)	358(86.9)	703(87.8)	0.006
No	36(9.3)	28(6.8)	64(8.0)	
Not known	8.0(2.1)	26(6.3)	34(4.2)	
How often is ITN treated, n (%)				
Never	147 (31.1)	126(29.2)	273(31.7)	0.26
Once a year	49(11.4)	41(9.5)	90(10.4)	
Once in 6 months	20(4.6)	22(5.1)	42(4.9)	
Not known	215(49.9)	242(56.2)	457(53.0)	
Reasons for child not sleeping under an ITN, n (%)				
Forgot	42(65.6)	35(77.8)	77(70.6)	0.001
Allergic to ITN	0.0(0.0)	0.0(0.0)	0.0(0.0)	
Did not sleep at home	18(28.1)	2.0(4.4)	20(18.4)	
Was used by others	4.0(6.3)	8.0(17.8)	12(11.0)	
Other malaria control measures				
IRS	2.0(0.4)	1.0(0.2)	3.0(0.3)	0.355
Mosquito repellent coils	37(7.4)	50(10.0)	87(8.7)	
Body mosquito repellents	1.0(0.2)	0.0(0.0)	1.0(0.1)	
Mosquito repellent spray	25(5.0)	16(3.2)	41(4.1)	
Traditional medications	2.0(0.4)	2.0(0.4)	4.0(0.4)	

4.3.3 Uncomplicated malaria, all-cause sick visits and hospital admissions by year

Overall, there were a total of 345 episodes of uncomplicated malaria during the follow up time, 278 (81%) of which occurred before the age of 14 months ('year 1'). These numbers slightly lower (n=309) when only microscopy or RDT confirmed cases were used (Table 4.8). The incidence rates in year 1 and year 2 were 35.3 and 17.0 per 100 child years respectively, $p<0.001$ for uncomplicated malaria and 32.0 and 14.5 per 100 child years for confirmed uncomplicated malaria, $p<0.001$. Comparison of microscopy between readers showed a good agreement of 91.2% between first and second reader (kappa statistic 0.687, 95% CI: 0.57,0.80). The majority of uncomplicated malaria infections (99.4%) were due to *Plasmodium falciparum*. In terms of sick visits, 112.3 new sick visits per 100 child years were made to a health facility in year 1 compared to 60.8 in year 2. This pattern was similar for severe malaria (23.7 episodes of severe malaria in year 1 vs. 12.5 episodes in

year 2); all-cause hospital admissions (16.5 admissions per 100 child years in year 1 vs. 12.5 admissions per 100 child years in year 2) and all-cause mortality (3.0 deaths per 100 child years in year 1 vs. 0.5 deaths per 100 child years in year 2) (Table 4.8). The leading causes of death were pneumonia (27.8%) among HIV_{ex} children and gastrointestinal symptoms (37.5%) among HIV_{un} children (Table 4.7).

Table 4.7: Causes of deaths in HIVex and HIVun children

HIV_{ex}	**Overall, n (%) N=26**	**$HIV_{ex,}$ n (%), N=18**	**$HIV_{un,}$ n (%), N=8**
Respiratory Tract Infections (Pneumonia)	7 (26.9)	5(27.8)	2(25.0)
Gastrointestinal symptoms (Malnutrition)	7(26.9)	4(22.2)	3(37.5)
Septicaemia	5(19.2)	4(22.2)	1(12.5)
Malaria	1(4.0)	1(5.6)	0
Haematological symptoms (Anaemia)	1(4.0)	1(5.6)	0
Unknown	4(15.0)	2(11.0)	2(25.0)
Neurological	1(4.0)	1(5.6)	0

Table 4.8:Cumulative risk and incidence of uncomplicated malaria, sick visits and admissions by group and by year

Outcome	[1]HIV_{ex}							[2]HIV_{un}						[8]Overall IR/Yr
	[3]Yr	[4]N	[5]CR %	Person days	Events	[6]IR/grp/Yr	[7]IR/grp	N	CR %	Person days	Events	IR/grp/Yr	IR/grp	
Uncomplicated malaria§	1	500	23.2	147817	116	28.7	24.8	500	32.4	139989	162	42.3	33.9	35.3
	2	473	7.2	73311	34	16.9		488	6.8	70344	33	17.1		17
Confirmed uncomplicated malaria¶	1	500	21.2	147817	106	26.2	22.1	500	29.2	139989	146	38.1	30.4	32.0
	2	473	5.9	73311	28	14.0		488	5.9	70344	29	15.1		14.5
Sick Visits	1	500	85.4	147817	427	105.5	90.8	500	91.6	139989	458	119.4	99.7	112.3
	2	473	26	73311	123	61.2		488	23.8	70344	116	60.2		60.8
Severe malaria	1	500	22.6	147817	113	27.9	23.5	500	14.8	139989	74	19.3	16.3	23.7
	2	473	6.1	73311	29	14.4		488	4.1	70344	20	10.4		12.5
Admissions	1	500	13	147817	65	16.1	16.2	500	13	139989	65	17.1	14.8	16.5
	2	473	6.1	73311	29	14.4		488	4.1	70344	20	10.4		12.5
Deaths	1	500	3.4	147817	17	4.2	3	500	1.4	139989	7	1.8	1.4	3.0
	2	473	0.2	73311	1	0.5		488	0.2	70344	1	0.5		0.5

[1]HIVex: HIV Exposed; [2]HIVun: non-HIV Exposed; [3]Yr: Year; [4]N: children at risk at start of observation period; [5]CR: Cumulative Risk; [6]IR/grp/Yr: Incidence rate per 100 child years per group per year; [7]IR/grp: Incidence Rate per 100 child years per group; [8]Overall IR/Yr: Overall Incidence Rate per 100 child years per year; **Definitions:** Year 1: ≤14 months; Year 2: 15-24 months; Events/group: Events per HIV_{ex}/HIV_{un}; IR/grp/yr: Incidence rate per group per year; Overall IR/yr: incidence Rate for each outcome for year 1 and for year 2. IR/grp: Incidence rate per group (HIV_{ex} or HIV_{un}); Uncomplicated malaria§: uncomplicated malaria that includes both laboratory and clinically confirmed malaria; Confirmed uncomplicated malaria¶: uncomplicated malaria that excludes clinically confirmed uncomplicated malaria.

4.3.4 Baseline characteristics associated with the incidence of uncomplicated malaria, in children during follow-up time in univariate analysis

The univariate analysis with the primary outcome (incidence of uncomplicated malaria) revealed a significant association with socio-economic status indicator factors such as use of electricity, main water source, dwelling roof type, father's education as well as occupation; and religion, body temperature, and presence of malaria parasites at baseline (Table 4.9). Having parasitaemia at baseline was significantly associated with a more than five-fold higher incidence of uncomplicated malaria (IRR 5.50, 95% CI 2.95, 10.28), $p<0.001$. Factors such as sex, anthropometric measurements including weight, length and MUAC; ethnicity, mother's age and job and history of a febrile illness were not significantly associated with the incidence of uncomplicated malaria.

Table 4.9: Univariate association of baseline characteristics with the incidence of uncomplicated malaria

Covariable	IRR	95% CI	P. Value
HIV Exposure			
HIV Exposed	Reference	Reference	<0.001
Non-HIV Exposed	2.91	2.05, 4.14	
Sex			
Male	Reference	Reference	0.585
Female	1.08	0.81, 1.44	
Age at enrolment	1	0.99, 1.01	0.867
Weight	0.97	0.98, 1.04	0.713
Length	1.01	1.01, 1.02	0.573
MUAC	1.03	0.93, 1.14	0.542
Temperature	1.3	0.85, 1.39	0.037
Haemoglobin level	1.01	0.99, 1.05	0.787
History of febrile illness			
Yes	Reference	Reference	0.82
No	0.93	0.50, 1.74	
Malaria parasites			
Negative	Reference	Reference	<0.001
Positive	5.5	2.95, 10.28	
Ethnicity			
Yao	Reference	Reference	
Other	1.17	0.86, 1.59	0.304
Religion			
Moslem	Reference	Reference	0.012
Christian	1.56	1.10, 2.21	
Use of electricity			
Yes	Reference	Reference	<0.001
No	2.28	1.63, 3.20	
Main water Source			
Tap	Reference	Reference	<0.001
Borehole	2.35	1.74, 3.16	
Stream	1.35	1.16, 11.47	
Unprotected well	1.72	1.10, 2.69	
Dwelling roof type			
Iron sheets	Reference	Reference	<0.001
Grass thatched	2.14	1.61, 2.85	
Roof tiles	0.28	0.05, 1.65	
Age of Mother	0.99	0.97, 1.02	0.464

Table continued

Table 4.9 continued

Mother's Education			
None	Reference	Reference	<0.001
Primary	0.92	0.48, 1.76	
Secondary	0.61	0.31, 1.20	
Tertiary	0.2	0.71, 0.54	
Father's Education			
None	Reference	Reference	0.027
Primary	0.89	0.61, 1.22	
Secondary	0.63	0.44, 0.88	
Tertiary	0.55	0.36, 0.84	
Mother's Job			
Employed	Reference	Reference	0.236
Not employed	1.36	0.82, 2.26	
Father's Job			
Employed	Reference	Reference	<0.001
Not employed	1.13	1.00, 1.37	

IRR: Incidence Rate Ratio; CI: Confidence Interval; HIV_{ex}: HIV Exposed; HIV_{un}: non-HIV Exposed; MUAC: Mid-Upper Arm Circumference

4.3.5 Univariate association of malaria control measures and the incidence of uncomplicated malaria

In terms of malaria control measures, the number of mosquito nets available in the household (net ownership) was significantly associated with the incidence of uncomplicated malaria. Children living in households with one or more mosquito nets had a 40% lower incidence of uncomplicated malaria compared to households without a mosquito net (IRR 0.60, 95% CI 0.42, 0.86), p=0.005. ITNs were associated with decreased rates of malaria relative to untreated nets (IRR 0.65, 95% CI 0.44, 0.96), p=0.030. Treating the nets once in six months was associated with a 65% reduction in the incidence of uncomplicated malaria while treating them once a year yielded a 14% lower rate (IRR 0.35, 95% CI 0.17, 0.69) and (IRR 0.86, 95% CI 0.48, 1.52) respectively, p=0.027. Having a child sleep under either an untreated mosquito net or an ITN during the previous night was not significantly associated with the incidence of uncomplicated malaria (IRR 1.00, 95% CI 0.57, 1.76), p=0.996 and (IRR 1.38, 95% CI 0.90, 2.13), P=0.166 respectively in the univariate analysis (Table 4.10).

Table 4.10: Univariate association between use of malaria control measures and the incidence of uncomplicated malaria

Covariable	IRR	95% CI	P Value
Number of mosquito nets in use in the home, n (%)			
0	Reference	Reference	
≥1	0.6	0.42, 0.86	0.005
Mosquito nets treated with insecticides			
No	Reference	Reference	0.03
Yes	0.65	0.44, 0.96	
Frequency of net treatment			
Never	Reference	Reference	0.027
Once in 6 months	0.35	0.17, 0.69	
Once in a year	0.86	0.48, 1.52	
Not known	0.79	0.53, 1.19	
Child slept under a net last night			
Yes	Reference	Reference	0.996
No	1	0.57, 1.76	
Not known	-	-	
Child slept under an ITN last night			
No	Reference	Reference	0.166
Yes	0.72	0.47, 1.11	
Not known	1.1	0.56, 2.18	
Other malaria control measures			
IRS	Reference	Reference	0.109
Mosquito repellent coils	4.55	0.86, 23.96	
Body mosquito repellents	14.87	1.77, 125.09	
Mosquito repellent spray	2.47	0.42, 14.43	
Traditional Medicines	1.84	0.15, 22.42	

4.3.6 Effect of CPT on uncomplicated malaria, sick visits, severe malaria, admissions and mortality

4.3.6.1 Uncomplicated malaria

Overall, the crude incidence rate for uncomplicated malaria during the follow up period was lower in HIV_{ex} children compared to HIV_{un} (24.8 vs. 33.9 episodes per 100 child years) P=0.004 (Table 4.8). Use of a confirmed uncomplicated malaria definition showed a similar trend (Table 4.8). Stratification by year and group showed that most of this difference occurred in the first year when HIV_{ex} were protected by CPT; (IRR 0.35, 95%

CI 0.25, 0.49), p<0.001, in multiple regression models adjusting for child factors such as presence of fever and parasitaemia at baseline and household factors including mother's education, mother's job, dwelling roof type and religion. However, the incidence rates in year 2 for the HIV_{ex} were similar to that observed in the HIV_{un} during the same period (IRR 0.94, 95% CI 0. 53, 1.68), P=0.839, thus there was no evidence for an excess risk of malaria in the HIV_{ex} group after the CPT was stopped. This difference in the observed IRR estimates in year-1 (0.35) and year-2 (0.94) was statistically significant (P-value interaction term, P=0.004) (Table 4.11). A similar picture was observed when a confirmed uncomplicated malaria definition was used.

4.3.6.2 All-cause sick child visits (all cause-morbidity)

During the follow-up time, the incidence of all-cause sick visits was slightly lower in HIV_{ex} group (90.8 compared to 99.7). However, in year-1, the incidence of all cause morbidity was 47% lower in the HIV_{ex} group compared to the HIV_{un} group (IRR 0.53, 95% CI 0.46, 0.60), p<0.001. Similar to the observations for uncomplicated malaria, the incidence in the HIV_{ex} group increased after stopping CPT (Table 4.11), but there was no evidence for an excess risk in year-2 after stopping CPT in the HIV_{ex} group as the rate remained slightly (not significant) lower relative to the HIV_{un} group (IRR 0.84, 95% CI 0.66, 1.08), p=0.171.

Table 4.11: The effect of before and after stopping CPT on the incidence of uncomplicated and severe malaria, sick visits, hospital admissions and mortality[1]

Outcome		Year 1 (6 weeks to 14 months)			Year 2 (15-24 months)			Interaction Term for difference between $^{3}HIV_{ex}$ and $^{4}HIV_{un}$ groups by year		
		IRR/RR	95% CI	P value	IRR	95% CI	P value	ITR_{IRR}	95% CI	P value
Uncomplicated Malaria✚	Unadjusted	0.33	0.22,0.49	<0.000	0.93	0.44, 1.97	0.852	2.82	1.23, 6.47	0.014
	Adjusted	0.35	0.25,0.49	<0.001	0.94	0.53,1.68	0.839	2.66	1.38,5.15	0.004
Confirmed uncomplicated Malaria★	Unadjusted	0.29	0.20,0.42	<0.001	0.89	0.41,1.62	0.867	2.80	1.19,6.59	0.020
	Adjusted	0.30	0.23,0.39	<0.001	0.91	0.43,1.93	0.841	2.64	1.35,5.16	0.006
All-cause sick visits	Unadjusted	0.54	0.48,0.62	<0.001	0.86	0.68, 1.10	0.236	1.59	1.22, 2.06	0.001
	Adjusted	0.53	0.46, 0.60	<0.001	0.84	0.66, 1.08	0.171	1.6	1.23, 2.09	<0.001
Severe malaria	Unadjusted	0.85	0.61, 1.19	0.349	1.56	0.79, 3.09	0.2	1.83	0.87, 3.84	0.11
	Adjusted	0.85	0.61,1.19	0.339	1.55	0.79, 3.07	0.206	1.83	0.87, 3.84	0.112
All-cause admissions	Unadjusted	0.47	0.26, 0.83	0.01	1.6	0.63, 4.08	0.328	3.42	1.41, 8.32	0.007
	Adjusted	0.46	0.26, 0.80	0.006	1.42	0.57, 3.56	0.444	3.12	1.32, 7.41	0.01
All-cause mortality[2]	Unadjusted	1.76	0.65, 4.82	0.267	-	-	-	-	-	-
	Adjusted	1.73	0.65, 4.67	0.275	-	-	-	-	-	-

[1]Models adjusted for HIV exposure, father's education, frequency of net treatment, child sleeping under an ITN in the previous night, temperature, malaria parasitaemia at baseline, age at enrollment, dwelling roof type, use of electricity, main water source, job of mother and religion

[2]All cause mortality is estimated using log-binomial regression using a Risk Ratio as a measure of effect; $^{3}HIV_{ex}$: HIV exposed children; $^{4}HIV_{un}$: non-HIV exposed children; IRR: Incidence Rate Ratio; RR: Risk Ratio, CI: Confidence Intervals,

Definitions: Uncomplicated malaria✚: uncomplicated malaria that includes both laboratory and clinically confirmed malaria; confirmed uncomplicated malaria★: uncomplicated malaria that excludes clinically confirmed malaria

4.3.6.3 Hospital admissions

In year-1, HIV_{ex} children on CPT had a 15% lower (not statistically significant) incidence of hospitalization due to severe malaria than their HIV_{un} counterparts (IRR 0.85, 95% CI 0.61, 1.19), p=0.339, and a significantly lower rate of all-cause hospitalisations (IRR 0.46, 95% CI 0.26, 0.80), p=0.006. Following the discontinuation of CPT in year-2 the incidence rate appeared higher in HIV_{ex} group than in the HIV_{un} group (malaria admission: IRR 1.55, 95% CI 0.79, 3.07, p=0.206; all-cause admissions: IRR 1.42, 95% CI 0.57, 3.56, p=0.444), but the differences between the groups were not statistically significant.

4.3.6.4 All-cause mortality

All cause mortality was estimated for the first year only because almost all events occurred during this period (24 out of 26 deaths). The log-binomial regression analysis showed a non-significant increase in the risk of mortality in the HIV_{ex} group in year 1 (RR 1.73, 95% CI 0.65, 4.67), p=0.275 after adjusting for age, mother's education, father's occupation, having child sleep under an ITN and religion.

4.4 Discussion

The primary objective for this chapter was to investigate whether HIV exposed children protected by CPT during their first year of life, have an excess risk of malaria (a rebound effect) after stopping CPT which might result from the potential for delayed acquisition of natural immunity to malaria (Osterbauer, 2012). Generally, uncomplicated malaria was markedly less common among the HIV_{ex} children while receiving CPT compared to HIV_{un} children not receiving CPT during that same period (the 12.5 month period from approximately 6 weeks to 14 months of age). The effects estimates were much the same when all clinically suspected cases were included in the analysis versus an analysis that was restricted to the diagnostically confirmed malaria only (90% of the overall sample). The small differences reflected the scale up of the use of malaria rapid diagnostic testing in all health facilities. In addition, these were study participants who were constantly reminded at every contact to report to the study clinic whenever they were sick rather than other clinics not involved in the study.

The chemo prophylactic effect of CPT was also associated with a significant decrease in the risk of all-cause sick-child clinic visits and hospital admissions. This study did not show evidence of increase in the incidence of uncomplicated malaria and all-cause morbidity (rebound effects) after CPT was stopped, although the rate of hospital admissions appeared higher in the HIV_{ex} than in the HIV_{un} children, but this difference was not statistically significant and could be more related to HIV exposure as opposed to CPT since these children were born to HIV infected mothers. The higher mortality among HIV_{ex} children during the time they were taking CPT suggest that either CPT had no impact on all-cause mortality, or that the benefits were too small to outweigh the anticipated increased mortality in this high risk group relative to HIV_{un} infants. Moreover, the mortality rate in this group falls below the general mortality reported among infants in Malawi in 2012 (UNICEF, 2013).

A major limitation of the study is the non-randomized nature of the study arms and the observed differences in risk factors for malaria between the study groups at enrolment, which limits firm conclusions about a causal role of CPT and might have resulted in biased estimates of the effect size of CPT (under or overestimate). However, there are

good reasons to believe that the beneficial differences observed during the first year are, at least in part, due to CPT. The magnitude of the effect size makes it plausible that this finding is not due to chance and there is evidence that CPT is an effective intervention for malaria prevention in both children as well as adults (Mermin et al., 2006). A double-blind randomized placebo-controlled trial of HIV infected children in Zambia showed similar effects (Chintu, 2004). Hospital admission rates decreased by 23% in HIV infected children who received CPT (Chintu, 2004). Cotrimoxazole's protective efficacy estimated against malaria ranged from 39% to 99.5% in previous studies conducted in different settings in Africa (Sandison, 2011, Gasasira et al., Dow, 2012, Thera et al., 2005). A meta-analysis of five studies on the effect of CPT on the prevention of malaria in children in SSA presented in chapter three of this report has shown that CPT even in the high presence of antifolate resistance still achieved a 63% reduction in the risk of malaria in children.

Our findings, in part, contrast with those from previous studies showing an increase in non-severe malaria and non-severe all-cause morbidity after the chemoprophylaxis is stopped (Aponte, 2007), but consistent with our results of higher hospital admissions. The lack of a rebound effect for uncomplicated malaria is perhaps surprising, because the high protective efficacy of CPT against uncomplicated malaria observed in this study (65%) might be sufficient to impair the development of naturally acquired immunity to malaria which is dependent on exposure to blood stage malaria infections (Doolan, 2009, Menendez et al., 1997). Compliance to CPT was closely monitored during the study and is unlikely the reason for the lack of rebound after a sustained period of malaria chemoprophylaxis. A possible explanation is that CPT alone provides incomplete protection and that even with CPT; children got exposed to some malaria infection allowing the acquisition of malaria specific immunity. This may be particularly the case in areas with high grade resistance to the antimalarial SP which is widespread in many parts of east and southern Africa including Malawi, which may partially impair the efficacy of CPT because of possible cross-resistance (Mbeye, 2014). However, the 65% protective effect observed in this study, contrasts with a more recent cotrimoxazole study in Uganda in which they got a lower protective effect of 39% in year one possibly due to very high prevalence of plasmodium genotypes associated with antifolate resistance (Sandison, 2011). The extended (4 years) use of CPT in a randomized clinical trial in Uganda also found no evidence for a rebound effect (Homsy, 2014).

The observed significant association of the incidence of uncomplicated malaria with baseline parasitaemia in the univariate analysis might be a reflection of a combination of factors such as high exposure to malaria infection due to location and household structure etc., as well as behavioral factors and host genetics.

The lack of a rebound effect against non-severe disease also agrees with the pooled analysis of six IPTi trials that used SP in different African settings in which a sustained protection against malaria was not seen following the last dose of SP-IPTi at 9 month of age, and continued follow-up up to two years of age did not indicate a rebound effect in infants who were assigned to IPTi during their first year of life (Aponte, 2009). The nature of IPTi which involves administering the treatment at intervals alongside EPI vaccinations allowed some degree of exposure to malaria infection in between treatments thereby allowing the infants to acquire some levels of natural immunity to malaria (Bijker, 2012). The lower usage of bed nets reported in these IPTi trials could also have exposed the children to infective mosquito bites and consequently allowing acquisition of natural immunity to malaria.

So how do we explain the lack of a rebound effect against uncomplicated malaria, yet there is some indication for higher rates of hospital admissions after CPT is stopped? This rebound scenario is similar to the one in a trial using IPTi-SP in Ghana which also showed no rebound of uncomplicated malaria but increased risk of severe malaria (Mockenhaupt, 2007). Is it possible that partial protection impairs the acquisition of protective immunity against severe disease, while allowing for enough infections to break through to allow for the development of immunity against non-severe disease? This scenario is unlikely, because typically the development of protective immunity in young children results first in a reduced risk of severe disease, followed later by a reduction in uncomplicated episodes. Another possible explanation for the observed phenomenon is potential confounding by indication as the nature of being exposed to CPT was not at random hence the indication for CPT in the HIV_{ex} group may be related to the risk of future health outcomes, the resulting imbalance in the underlying risk profile between the HIV_{ex} and HIV_{un} group may generate such results.

A major limitation of our study was the non- randomized design and use of a control group that a priori was likely to have less morbidity overall than HIV_{ex} children, at least in the absence of any intervention such as CPT. HIV exposure in HIV_{ex} but not infected children has been associated with increased congenital as well as maternally acquired neonatal infections which are thought to be caused by the increased shedding and high pathogen levels related to immunosuppression in the mother (Kuhn, 2005). It is plausible that this increased exposure to pathogens in HIV_{ex} children is sustained into the 2^{nd} year and could explain some of the differences in severe morbidity in year-2. Nevertheless it remains unclear why these findings are only observed for the severe endpoints and not for non-severe disease. It is also possible that the increase in severe malaria in year two was simply due to chance as evidenced by lack of statistical significance. The decline in susceptibility to malaria infection during the time HIV_{ex} were receiving CPT may have contributed to an enhanced risk of severe disease when CPT had been stopped. This is suggested to affect the rate of the disease adversely by delaying the average of first infection thereby reducing the enhancement of the immunity that may be necessary for the maintenance of immunity to severe malaria (Gupta, 1999). Nevertheless, we cannot completely rule out the possibility of rebound effects considering that the follow-ups are on going and although not statistically significant, there is some evidence suggestive of increase in the incidence of uncomplicated malaria and all-cause morbidity as the effects were more diluted in year 2 after CPT was stopped. Although not ethically appropriate, randomizing HIV_{ex} children into receiving and not receiving CPT would have ensured an even distribution of participants in terms of baseline biological characteristics and therefore provide the true effect of cotrimoxazole prophylaxis on malaria, this is debatable as malaria incidence seemed to be reduced in the HIV_{ex} group compared to HIV_{un} group. This may imply that HIV exposure may not significantly influence the measure of effect that was obtained. Furthermore, absence of significant differences in the malaria incidence in year 2 when HIV_{ex} children had stopped CPT and breastfeeding compared to their HIV_{un} counterparts who continued breastfeeding until beyond the age of 12 months, contrasts with the findings from Tororo in Uganda, a high malaria transmission area which showed a significant reduction in the risk of getting malaria with breastfeeding in children aged six to 15 months (Vora et al., 2010). The small numbers in year 2 as the study was still on going might have contributed to the observed findings.

The lack of data of CD4+ counts for mothers of HIV infected children in this study limits the interpretation of the findings since maternal CD4+ is a major determinant of a child's health (Kuhn, 2002). However, the observed high protective efficacy of CPT in HIV exposed children would be linked to widespread use of antiretroviral drugs among mothers in the PMTCT programme which might have improved the health status of HIV infected mothers making it comparable with HIV negative mothers. However, the lack of performing an HIV test on all the mothers of children participating in this study to confirm their sero-status, could have led to misclassification of maternal HIV status which might have contributed to the observed findings. If more women were misclassified as HIV infected, the observed effect might be an overestimation of the effect of CPT in the HIV_{ex} and an underestimation of the effect in year 1 in HIV_{un} if more women were misclassified as HIV negative. On the other hand, the overall shorter follow-up period in HIV_{un} children might have affected the measurement of the primary outcome of interest in that lesser events might have been captured in the HIV_{un} group compared to the HIV_{ex} group which was followed up for a relatively longer period of time. This limitation is likely to be addressed at the end of the study when all groups will have completed their study follow-up time. Additionally, the inclusion of an offset in the analysis accounted for the differences in the follow up time hence the observed measure of effect might not have been affected by the differences in follow-up time.

Interestingly, more HIV_{ex} children had access to safer water supply; better housing conditions and electricity, which were strong determinants of uncomplicated malaria in the univariate analysis. The strong association with better housing conditions including better water source, iron sheet or tile roofed houses and using electricity validates recent findings in a study in Korogwe, Tanzania where quality of housing significantly reduced the risk of malaria by one-third apparently due to the tendency of good quality houses to reduce number of malaria vectors (Liu, 2014) by restricting mosquito entry thereby reducing human exposure (Osterbauer, 2012). Other studies in Malawi (Wolff, 2001) and Burkina Faso (Ye, 2006) have found similar findings and across the region in Sri Lanka, Gamage-Mendis *et al* also observed that living in a house that was complete, built with bricks, plastered wall and roofed with tiles was a strong determinant of reduction in malaria risk compared to living in the poorest type of houses (Gamage-Mendis, 1991). Roof type is thought to determine indoor temperature, a parameter that is associated with malaria transmission (Ye, 2006). Although it is unlikely that housing conditions would

solely have affected the incidence of malaria in the present study because the whole study catchment area was semi urban with very minimal diversity in the form of housing, the finding is an important contribution to inform identification of interventions for malaria control in many settings in Malawi.

ITN use has been associated with a reduction of malaria infection in people of all ages and this study also showed a protective association with ITN ownership and with the frequency of treating the nets with insecticides, although most households were using LLINs (MoH, 2012). This relationship could possibly explain the sustained protective effect of ITNs when a child slept under it in the previous night compared to sleeping in any net. The reasonably better ownership and utilization of mosquito nets in the present study surpassed national figures in which only 60% of the household owned at least one net and 56% of children aged under the age of five slept under an ITN in the previous night respectively (MoH, 2012). The high figures observed in this study could be a good indicator of progress being made on the realization of the goals of 2011-2015 malaria strategic plan which set out to achieve universal access to malaria control interventions by 2015 (MoH, 2011b). Moreover universal distribution of LLINs throughout the country preceded the current study.

While some studies have reported association between anthropometry and malaria morbidity (Genton, 1998) most studies have reported inconclusive results (Deribew) suggesting lack of consensus on the effect of anthropometry on malaria. The lack of association between the incidence of uncomplicated malaria and anthropometry in this study is in agreement with findings by Snow et al in which poor nutritional status was not associated with susceptibility to malaria in Gambian children (Snow, 1991).

4.4.1 Summary of discussion

Overall, we found that CPT was associated with marked reductions in the incidence of uncomplicated malaria and all-cause sick child clinic visits and hospital admissions. There was no evidence that the risk of malaria increased in the 2nd year after cessation of CPT at 14 months of age. The present study is still ongoing, and the current analysis included only about 60% of the potential follow-up time in year 2. Although this is unlikely to impact on the findings in the first year, the interpretations of the findings in the second year should be made with caution. This is especially the case for the less frequent endpoints such as hospital admission and deaths for which the power of the existing

sample was still limited. Thus it remains to be determined whether the clear benefits observed with CPT in the first year are outweighed by a potential increase in the risk of hospital admissions in the 2nd year. More definitive results will be available following completion of the follow-up by August 2014.

CHAPTER 5 : LIVED EXPERIENCES OF HIV INFECTED MOTHERS ADMINISTERING DAILY COTRIMOXAZOLE TO THEIR HIV EXPOSED BUT UNINFECTED CHILDREN

5.1 Introduction

5.1.1 The use of Cotrimoxazole prophylaxis in HIV exposed children

Administered once daily, cotrimoxazole prophylaxis (CPT) has become an important component of HIV care and treatment package for HIV exposed children following WHO recommendations that all children exposed to HIV should receive this prophylaxis from about 4 to 6 weeks of age until they stop breastfeeding and HIV infection is excluded (WHO, 2006b). This is an antimicrobial drug that prevents the development of serious, often fatal Opportunistic Infections (OIs), notably *Pneumocystis jiroveci* pneumonia (PCP) in young HIV-infected infants (WHO, 2006b). Most importantly, CPT has previously been found to be an effective antimalarial in both adults and children (Mermin et al., 2006, Sandison, 2011). In chapters three and four of this report, the use of CPT in children showed a more than two-thirds reduction in new malaria infections in children. Other studies have shown that its effectiveness remains even with the presence of widespread background resistance to it (Sandison, 2011). This is especially important given the numbers of children dying of malaria in Africa. In 2013, more than three-quarters of all the malaria deaths in Africa occurred in children under five years of age (WHO, 2013b). In order to achieve optimal benefits from CPT, strategies for adherence and coping with various challenges associated with long-term treatments must be achieved. However, it is not known how the long-term administration of CPT would impact on the lives of HIV infected women with HIV exposed but not infected children.

Benefits to be realized from CPT are particularly important in resource-limited settings where access to effective services for prevention of mother-to-child transmission of HIV, effective infant-feeding interventions, early diagnostic services and antiretroviral therapy (ART) for children remain limited yet despite the fact that countries have developed and put in place policies to support the scale up and implementation of CPT for infants and children, and that it is inexpensive, life-saving, safe and theoretically simple to deliver, a few children (8%) exposed to HIV were initiated on CPT by two months of age in 2008 (WHO, 2010d), a situation that could affect health outcomes in these children. Understanding the experiences of mothers administering CPT to their HIV exposed but uninfected children would provide an understanding of how mothers cope in terms of ensuring compliance to the intervention as well as how they deal with any situations that arise eventually leading to improved uptake of the interventions.

5.2 Study Objectives

1. To establish a narrative of the lived experiences of HIV infected women administering daily CPT to their HIV exposed children
2. To explain how HIV infected women's lived experiences, attitudes and life circumstances impact on their behaviours towards administering CPT to their HIV exposed but not infected children.
3. To identify factors associated with uptake of CPT in HIV exposed but not infected children

5.3 Methods

Narrative approach was used to understand lived experiences of HIV infected mothers administering CPT to their children who are not infected with HIV. The use of open-ended questions and probing of their initial responses were used to enable them to respond in their own words ultimately providing stories that explain their experiences and from these stories; society, family and household dynamics related to administering CPT in HIV exposed children were identified using grounded theory approaches to build a theory that explains CPT adherence in children.

5.3.1 The narrative approach

The narrative approach is a process of gathering information through story telling (Chataika, 2005). This approach was chosen because it gives insights into the experiences and realities of people being studied (Goodley, 2000) hence forms the central component of experience and reality. It is understood as an approach that includes a temporal ordering of events and the researcher makes an effort to make points out of those events (Sandelowski, 1991). The narrative framework allows researchers to have special access to the human experience of a situation (Sandelowski, 1991) and is concerned with the storied nature of an experience from an insider view point (Bruner, 1986). In narrative analysis, the coding is typically of the narratives as a whole, unlike other methods that use different elements within the narratives. The coding strategy revolves around reading the stories and classifying them into general patterns.

5.3.2 The Grounded theory approach

In this study, grounded theory techniques were partially applied to explain how the women's lived experiences, attitudes and life circumstances impact on their behaviours towards administering CPT to their HIV exposed but not infected children. Grounded theory methodology is an approach in which the researcher first goes into the field and builds a theory from the findings as they go along in the research (Straus, 1998). It is most commonly used in research areas that have hardly been explored. It seeks to guide researchers in producing theory that can explain the "patterns of actions and interaction between and among various types of social units" (Strauss and Corbin, 1998, Straus, 1998). The theory construction operates within the framework of the specific context and is thus flexible and fluid to realise that situations change and each situation is unique and requires fresh exploration. Ultimately, grounded theory will build a theoretical explanation of the poor or good adherence to CPT by helping us understand the conditions necessary to give rise to these phenomena, how it expresses itself through action and interaction and the consequences that result from them. There has been a lot of debate in the literature on the approach to grounded theory since the divergence in views on approach by Glaser and Strauss, the two pioneers of grounded theory (Glaser, 1992, Strauss, 1990) occurred.

Since this study aimed at eliciting experiences with administering CPT to HIV exposed children who are 'presumably healthy children,' the Glaserian approach seemed suitable to explore this area that has hardly been explored. The Glaserian approach allowed natural observation and elicitation of this information from the stories told by the HIV infected women administering CPT to their HIV exposed but not infected infants and allowed for the development of patterns of their experiences and concepts that explain such a situation. This being an area that has never been researched, the combination of narrative and grounded theory approaches allowed the mother to tell their experiences from which theoretical concepts explaining actions adopted by mothers administering daily CPT to their children emerged in contrast to the commonly used framework approach which lacks the ability to generate social theory (Gale, 2013).

5.3.3 Study participants and Sampling

The study participants were HIV infected women with young children participating in a large cohort study aimed at investigating the effect of stopping CPT on malaria, other

morbidities and mortality. Participants were randomly selected from three groups: a group that had just started administering CPT; another group in the middle of giving CPT and the third one at end of the CPT period. These participants were purposively sampled from a cohort of mothers who had their children participating in a large cohort in order to reach the targeted sample size quickly considering the limited academic time and financial constraints. Every two months, study participants were visited in their homes for a refill of CPT for their children as well as counseling on adherence to treatment. However, as data collection progressed, the selection of participants for IDIs followed a theoretical sampling suggested by Glaser and Strauss. Theoretical sampling aims at including participants on the basis of an understanding of the context, emerging concepts from on-going data analysis and a deliberate attempt to 'test' such concepts (Crabtree, 1999). Firstly, participants for FGDs were selected using purposive sampling as explained above. However, as data was being collected and concepts begun to emerge, there was need to sample more educated mothers to aid saturation of data as majority of women in the FGDs had primary education (Crabtree, 1999). Consequently, more women who attained secondary school education were sampled for the IDIs (Table 2). The interview guides were constantly modified based on the responses from the interviews. This was made possible within a short period of time because all the participating women were part of an on-going large cohort study of cotrimoxazole prophylaxis and malaria (Chapter 4) in which they had provided informed consent at the onset to be included in the qualitative study. In addition, before taking part in the qualitative study, all participants were individually reminded of their participation in the FGDs and IDIs and were informed about the nature of the questions to be discussed which were likely to disclose their HIV status to other participants (especially for FGDs) and what was expected of them. Participants were free to withdraw from participation at any point they wanted.

As this is a qualitative study the sample size for the narrative cohort was 17 mothers of HIV exposed children. There were three FGD cohorts of between 6-12 women each which is a reasonable number to hold a discussion (Watts, 1982).

5.3.4 Ethical Considerations

This being part of the large cohort study from which the women came from, ethical approvals were sought together with the cohort study. The women were informed during the consenting process at the beginning of the cohort study about the likelihood of being

selected for this (qualitative) study at a later date implying that providing informed consent for the cohort study also meant consenting for this study hence ethical approvals for this specific study felt not to be required.

5.3.5 Data collection topic guides

Two separate data collection guides (Appendix 14 and Appendix 15) using open-ended questions were developed to guide In-depth interviews and FGDs respectively. A deductive approach based on ecological theory of perception influenced the formulation of the structured questions used in this study. The ecological theory was used because it is a general theory of the perception and control of behavior as it aspires to describe, explain and predict perception and action by all animals in all situations (CEHD, 2014) It focuses on the perception and behavior that occur naturally (CEHD, 2014). In addition to these questions, some thematic topic areas of exploration were evolving alongside the process of data collection throughout the interviews. In order to avoid inaccuracies, the data collection tools were translated into the local language, Chichewa. An independent person who did not participate in Chichewa translation did the back translation from Chichewa to English. This was done to ensure that the meaning was correct. Adjustments to the data collection topic guides were constantly made throughout the data collection process depending on the nature of discussions.

5.3.6 Data Collection methods

In this study, two data collection methods were used: In-depth Interviews and Focus Group Discussions. The combination of these two methods complimented each other in generating concepts and understanding participants' experiences, views, perceptions, values, beliefs and expectations about CPT adherence in HIV exposed children (Patton, 2002b, Robinson, 1999).

Demographic characteristics such as age, educational status, area of residence and occupation of the mothers of HIV exposed children were extracted from the cohort study of CPT and malaria database in which HIV exposed children were participating. Note taking and tape recording were used to collect and record the data respectively.

5.3.6.1 In-depth Interviews

Boyce C., et al, defines In-depth interviewing as a qualitative research technique that involves conducting intense individual interviews with a small number of respondents to

explore their perspectives on a particular idea, program or situation (Boyce, 2006). IDIs allow the interviewer to dig in deeply into social and personal matters. This makes it more advantageous than FGDs where digging deeply into an individual is prevented because of its public nature where an interviewer is only allowed to get a wider range of experiences from a group (Watts, 1982). IDIs were conducted with individual HIV infected mothers of HIV exposed children taking part in the large on-going cohort study of CPT and malaria.

5.3.6.2 Focus Group Discussions

Focus Group Discussions on the other hand involve a group of about 6-12 people who have similar experiences or concerns who come together to discuss a specific issue with the help of a facilitator in a setting where participants feel comfortable enough to engage in a dynamic discussion for one or two hours usually consisting of a mixed group of participants from different social backgrounds who do not know each other (Liamputtong, 2011, Green, 2014). This method allows researchers to uncover aspects of understanding that often remain hidden in the more conventional in-depth interviewing method (Liamputtong, 2011). In this study, FGDs were conducted with HIV infected women who had their children participating in an on going large cohort study of CPT and malaria with the aim of understanding their experiences with giving daily CPT to their children who are not infected with HIV but were still breastfeeding. For each FGD, there was one facilitator, a note taker and a researcher. The facilitator's responsibility was to guide the discussion using appropriate probes for depth and clarification throughout the process and ensured that tape-recording of the discussion was being done. The note taker concentrated on taking note of any non-verbal communication and gestures while the researcher was writing memos from the data to start building concepts for the development of the theory. The researcher constantly liaised with each one of the other team members as necessary to ensure that appropriate information was being collected.

5.3.7 Interviewing

One-on-one IDIs with mothers of HIV exposed children were conducted in a private room away from traffic to ensure privacy. Questions were asked using the local language in a non-judgemental manner and mothers were allowed to speak freely in the local language. Each IDI was completed between 30-45 minutes while each FGD lasted for about 1 hour and 45 minutes. Information on household decision-making on health issues, experiences with providing CPT to a child, perceptions about CPT provision to a child, and sources

and mode of provision of information on CPT was solicited. All discussions were tape-recorded accompanied by note taking of important highlights.

5.3.8 Data Analysis

A mixture of qualitative data analysis approaches was used to analyse the data. Themes were developed through a framework approach in which a systematic search for patterns to generate full descriptions of HIV infected women's experiences of giving daily CPT to their children was done. This helped to provide narratives that answered the question of the impact of the CPT programme on the women. Grounded theory approach was simultaneously applied to constantly develop emerging concepts from the themes and narratives across the women in order to refine the themes and develop a social theory explaining factors related to women's behavior related to administering CPT to their children. Furthermore, an inductive approach allowed for the unexpected and more socially located responses from the participants.

Although framework approach was used to identify emerging themes from the data, theoretical concepts to explain how the upcoming/emerging themes influenced some behaviors were identified simultaneously with data collection. Furthermore, as data was being collected, it was immediately being transcribed and analysed (Jones, 2011). Coding of important topics relevant to the subject was done in order to build a list of relevant topics that arose from both IDIs and FGDs (Jones, 2011). This process resulted in a series of categories and codes that helped build the phenomena arising from the study. All newly collected data was constantly compared with data collected previously. The analysis was aided with the use of N Vivo software version 10.0 (International, 2010). Meanwhile, classification and categorization of different categories were being made.

5.3.9 Trustworthiness of the data

Trustworthiness of the data is achieved when the research data is credible, transferable, dependable and confirmable (Lincoln, 1985). In this study, trustworthiness was achieved through triangulation by: (a) use of two approaches of data collection – IDIs and FGDs which provided the opportunity to look at emergence of different concepts from both individual and societal perspectives; (b) use of different researchers with different experience to conduct the one-on-one interviews and moderate FGDs. The comparison of interviews showed similarity in the issues that were emerging that reflects both dependability and confirmability of the data. The FGDs and IDIs were conducted by

individuals employed to work in the cohort study but with no direct interaction with study participants. These included Laboratory Technicians, Data Officer and a research intern working on quality assurance for other studies within the institution. These were trained and assigned to carry out the interviews in the local language, Chichewa. However, the responses were transcribed using English by the main researcher and the intern. During this process, the main researcher reviewed the type of probing and responses that were obtained. At a very early stage and throughout the data collection process, the main researcher engaged interviewers/moderators in discussions on proper probing on various topics. A sub-set of the translated transcripts was translated back in to Chichewa by an independent person and was compared with the original transcripts to identify any problems with translation. An independent expert social scientist reviewed some of the transcripts at random and provided support and guidance on the coding framework.

5.4 Results

5.4.1 Characteristics of study participants

5.4.1.1 Participants for Focus Group Discussions

Three FGDs were conducted with mothers of HIV exposed children receiving daily CPT taking part in an on-going large cohort study of CPT and malaria in HIV exposed children. In total, twenty-six women participated in the FGDs. Of these, five had attained secondary school education while the rest attained primary education (PE). The age of participants taking part in the FGDs ranged from 20-41 years. In terms of employment, the majority (24 out of 26) were unemployed (Table 5.1).

Table 5.1: Details of respondents who participated in FGDs

Focus Group Discussion 1				
FGD No.	**Age**	**Location**	**Education Level**	**Occupation**
1	23	Mikuyu	Primary	Security Guard
2	21	Mikuyu	Primary	Unemployed
3	20	Thabwani	Primary	Unemployed
4	38	Magumba	Primary	Unemployed
5	26	Chidzalo	Primary	Unemployed
6	31	Seven miles	Primary	Unemployed
7	28	Mpunga	Secondary	Business
8	31	Maonga	Primary	Unemployed
9	41	Six miles	Primary	Unemployed
10	27	Six miles	Primary	Unemployed
11	22	Magumba	Primary	Unemployed
12	28	Nambesya	Secondary	Unemployed
Focus Group Discussion 2				
1	34	Chiphola	Primary	Unemployed
2	40	Thabwani	Primary	Unemployed
3	23	Mpunga	Primary	Unemployed
4	29	Thom Allan	Secondary	Unemployed
5	29	Chikowi	Primary	Unemployed
6	24	Chikanda	Primary	Unemployed
Focus Group Discussion 3				
1	30	Mtiya	Secondary	Cleaner
2	38	Cobbe Barracks	Primary	Unemployed
3	32	Chikanda	Primary	Business
4	36	Six miles	Primary	Unemployed
5	35	Chinamwali	Primary	Unemployed
6	34	Namarika	None	Unemployed
7	36	Six miles	Secondary	Unemployed
8	33	Chikanda	Primary	Unemployed

5.4.1.2 Participants for In-depth interviews

Seventeen IDIs with mothers of HIV exposed children receiving daily CPT were conducted to obtain information on factors that influence adherence. The participants' ages ranged from 17-39 years. These participants were slightly younger than those in

FGDs. In addition, the majority of IDI participants (11 out of 17) were more educated having attained up to secondary education (SE) (Table 5.2).

Table 5.2: Details of respondents who participated in IDIs

IDI No.	Age	Location	Educational level	Occupation
1	24	Njonjo	Secondary	Unemployed
2	17	Nkoloma	Secondary	Unemployed
3	34	Namonde	Secondary	Unemployed
4	31	Chongo	Secondary	Unemployed
5	35	Chikanda	Secondary	Unemployed
6	39	Saile	Secondary	Unemployed
7	31	Peter Mtende	Secondary	Unemployed
8	33	Nkhalola	None	Unemployed
9	23	Cobbe Barracks	Secondary	Business
10	33	Kazembe	Primary	Unemployed
11	35	Chongo	None	Unemployed
12	33	Mpakati	Primary	Unemployed
13	20	Chizalo	Primary	Unemployed
14	29	Mpakati	Secondary	Unemployed
15	24	Kazembe	Secondary	Unemployed
16	29	Prison lines	Secondary	Unemployed
17	31	Saidi	Primary	Unemployed

5.4.2 Participant narratives of their lived experiences of administering daily CPT to their HIV exposed children

This section presents mothers' narratives of their experiences with administering CPT to their young children. The narratives reveal the impact of being in the programme and its influence on household dynamics; impact of access to information as a result of participating in the study (the main cohort study) and how it influences household and individual decision making on health; strategies HIV infected mothers with HIV exposed children employ to continue administering CPT to their HIV exposed children; motivating as well as deterring factors for continued administration of CPT and the role of support systems in the whole process. In addition, factors that influence adherence as well as a theoretical explanation of adhering to PMTCT interventions such as administering to daily CPT in HIV exposed but not infected children has been presented.

5.4.2.1 Impact of the PMTCT Programme on household dynamics

Impact on health decision-making powers in the household

Being in the PMTCT programme where women were administering daily CPT to their HIV exposed children modified decision-making powers within their households. Although most mothers indicated their spouses, parents and themselves as decision makers on health issues in general, in most instances decisions were made jointly between the spouses although there is an indication from the data that the influence in decision making was being dominated by those with economic power within the household with ten participants citing men as having more decision-making powers by virtue of being household heads. One married woman described how health-related decisions were made and implemented in her household:

> *"When the spouse is there, he encourages you to go to the hospital. As it is, it is the mother who takes the child to the hospital, the father just speaks of what ought to be done but he does not go with you. An exception only applies to loving husbands who may accompany you but it is women three quarters of the time"* (Respondent 010, IDI)

As would have been expected in most African settings where some men shun away from household health issues, it was interesting to note the reversal of this cultural norm in some households where male partners were not detached from household health issues as they actively participated in ensuring that their child was healthy as demonstrated in the quotation below.

> *"Ah, only that his father is very attentive. Usually when the child, say coughs, he instructs me to go with him to the clinic"* (Respondent 014, IDI)

Moreover, the quotation above clearly demonstrates the decision-making power by the husband while the wife plays the role of an implementer. However, in certain instances women disrespect these role boundaries and execute decisions without the knowledge of the husband. The woman in the quotation below narrates how she makes decisions on health and informs the husband afterwards:

> *"Anything that may happen to me or the child has to be reported to the spouse because he has to know since we are a family… When am back I tell him that the*

child is sick and I took him to the clinic, likewise when it is me, I call him and may tell him that I went to the hospital because I have malaria" (Respondent 011, IDI)

When asked as to whether the household decision maker on health issues influenced participation in the PMTCT programme and eventually the process of administering CPT to the child, participants unanimously indicated that they do not influence this process. Some women mentioned that if their spouses were to tell them not to give their child CPT, they would be doing it covertly without their knowledge. The dialogue in Table 5.3 illustrates the determination of one woman to continued administration of CPT irrespective of what the spouse said.

Table 5.3: Participant views on decision-making on health issues (Respondent 010, IDI)

Interviewer	Respondent
…….	*Am not affected negatively*
What if your husband decides that you should stop?	*I would not bend to that*
Why?	*Stopping the administration of Bactrim[§] (CPT) is tantamount to inviting problems*
Why not, it is the decision maker who has spoken?	*He cannot speak like that*
What if he does?	*Then I can always give him when my husband has left*

Four participants who stated that they were responsible for making decisions on health issues in their households, they were either not married or their spouses were not concerned about health issues of the household. Two of IDI participants indicated that their parents were the primary decision makers because they were dependent on them.

5.4.2.2 Impact of access to health information on household decision-making

Households look up to Health workers for information on CPT

Most study participants explained that they received adequate information regarding administering CPT to their children from health workers. They pointed out that the frequent reminders each time they interfaced with medical personnel at the study clinic enabled them to comply with interventions for their HIV exposed children such as administering CPT on daily basis. Some clients stated that they were visited once every two months while others mentioned that they visited the clinic themselves once in a while for drug refills when the Research Assistants (RAs) did not visit them on their scheduled date. However, under normal circumstances visits to the clinic were made either when the child was ill or the study clinic had requested them to do so as per the CPT and malaria study protocol.

> *"The information is enough ……. we receive it every time. When the doctors visit us, they remind us, 'do you give this child the treatment?' Then we respond saying,*

[§] Bactrim is a brand name for Cotrimoxazole (sulfamethoxazole-trimethoprim)

'yes, we give him,' and sometimes they also add onto the treatment." (Participant 003, FGD 2, Age 23, PE, Mpunga, Unemployed).

The three most preferred sources of CPT information mentioned by study participants included study clinic or the hospital; the media and home visits by health workers. These were also listed as main sources where the women got CPT information. Some people indicated community leaders and community groups, leaflets and telephones as potential sources of CPT information.

"The only way I can help my child is by coming to the clinic on the dates that have been allocated for me. … no other better place than the hospital. …the nurse, she is the one I can trust." (Respondent 011, IDI).

Adequacy and usefulness of information on CPT supports household decisions on health

Looking at perceptions about CPT information provided by health personnel, participants mainly perceived the information to be adequate as described below.

"The information is adequate, but at first we were not certain that bactrim was helpful for children. But as soon as they had informed us, "We are providing this bactrim for this child so that he doesn't get sick regularly," we accepted the information and made use of it, and now we have seen that this thing is very powerful." (Participant 003, FGD 2, Age 23, PE, Mpunga, Unemployed).

In terms of its usefulness, the women mainly considered that CPT information equipped them with appropriate knowledge and skills for safeguarding and protecting their children from various illnesses and HIV infection. Study participants also indicated that the information did not only allow them to make informed decisions about the wellbeing of their children in terms of making health-related choices, it also encouraged them to seek medical care from formal healthcare facilities in the event that the child was ill. Lastly, frequent provision of CPT information was perceived to act as reminders to parents when they had forgotten something related to CPT.

"Most of us forget and when we watch on Television we are reminded. I have benefited because in those times I was forgetting, it was there to remind me." (Respondent 009, IDI)

"This information has helped me because when I go for ANC visits, I see how well the child is gaining weight because he is receiving the proper care". (Respondent 011, IDI)

5.4.2.3 Motivation for continued administration of CPT to young children

A child's good health as a motivation for continued administration of CPT

Looking at what made women continue administering CPT to the HIV exposed child who was not infected, most participants indicated that they find this necessary because breastfeeding was ongoing. They continued providing CPT to their children in order to help prevent transmission of HIV from the mother through breastfeeding. Interestingly, respondents indicated that a true HIV status of a child could only be determined two years after birth hence stopping CPT would have meant exposing the child to risks of infections at a time when the parent is not sure of the child's true HIV serostatus as described below.

"I continue because even though he can be HIV negative, he is still at risk of being infected [with HIV] because he is breastfeeding. Then I continue with bactrim so that he should renew his strength." (Respondent 008, IDI)

The mothers felt it was necessary to provide CPT to a child who was HIV exposed but not infected in order to preserve good health of the child. There were fears that stopping administering CPT to a child may increase the child's vulnerability to diseases. However, one respondent indicated that it was not necessary to provide CPT to a child who is not infected with HIV yet, but did not provide reasons for this.

Most participants perceived the administration of CPT to a child as very important. The main reason provided was that CPT did not only improve immunity of the child but it also allowed the child to enjoy a good health. Participants felt that with CPT, the child did not fall sick frequently but it also made the illness less severe. Administering CPT was perceived to protect the child from infections including HIV infection, malaria, pneumonia, diarrhoea and cough as the two women narrated:

"The bactrim helps us to protect our children from getting ill often. Even coughs stay away from them; they are never frequently sick from them. Even when they are attacked by a cough, it never seriously gets them down. It is moderately different from someone who is not taking bactrim; it comes a bit harder." (Participant 002, FGD 3, Age 38, PE, Barracks, Unemployed)

"It is important because for a child who is on bactrim; He is not frequently attacked by malaria and for the pneumonia that was common before, he wasn't affected. Even the diarrhoea that accompanies teething, he did not have any. This is how I can explain the importance of bactrim." (Respondent 013, IDI)

The women provided testimonies that their children were growing as healthy as those of HIV negative women. Some observed that there was a big difference in terms of good health between their children and those belonging to other HIV positive women who were not receiving CPT.

"The child equally grows like those who are not from infected mothers and you cannot even differentiate their health. …administering bactrim to my child is very important. To begin with, bactrim protects the child from contracting the virus from the mother or even the prevention of being attacked by these other different insignificant diseases." (Respondent 004, IDI)

Participants also indicated that it was important to administer CPT to their children in order to improve their health. Providing CPT was equated to protecting the life of the child from HIV and thus improving longevity. Finally, some women indicated that CPT was saving the time and resources the parent would have spent by frequently visiting the hospital every time the child was ill.

"You are saved from frequenting the hospital because of the child's constant illness as is the case with the other children who may even suffer from serious illnesses." (Respondent 004, IDI)

Demonstration of compliance to medical advice/instructions

Continued provision of CPT to an HIV exposed child was also done to demonstrate compliance to the instructions provided by health care workers. Women were therefore merely acting upon the instructions given and were unable to act differently without receiving instructions to do so by the healthcare providers. To some, this compliance was reinforced by the fear of being humiliated once they go against healthcare workers' instructions. However, to others, being shouted at by the healthcare provider was not an issue to worry about if instructions have not been adhered to. The quotations below described how women trusted instructions from health professionals:

"You have to keep on offering the child bactrim even though he is seemingly healthy because the medical people haven't told you about the situation of his health. You can stop only when medical people have instructed to do so." (Participant 002, FGD 3, Age 38, PE, Barracks, Unemployed)

"No one will stop [a child] being on the treatment unless you instruct her to do so. On her own, she can't make that decision. She wants to hear from your [providers] mouth saying, "You should now stop offering the child [bactrim]." (Participant 006, FGD 3, Age 34, PE, Namarika, Unemployed).

Trust in healthcare providers

Most participants indicated that they trusted and followed instructions provided by health providers. Continued interaction with health providers reinforced the need to adhere to treatment as described by one respondent in a group discussion.

"We follow the required procedure which they give us at the hospital. We should not make the child skip [treatment]. We need to administer bactrim, half pill, to him daily, every morning. So, we implement the instruction from the hospital. If they tell us [something], we follow it." (Participant 008, FDG 3, Age 33, PE, Chikanda, Unemployed)

Willingness to improve health of the child

Some participants indicated that they adhered to CPT in order to protect their children from diseases. One participant in particular, indicated that she adhered to giving CPT to her child because she was still breastfeeding. She therefore felt that discontinuing treatment or non-adherence to treatment would increase the chances of her child acquiring HIV infection. CPT was thus viewed to protect the child from an HIV infection as narrated in the quote below:

"Because the child is still breastfeeding, I don't know how, but there is a risk of transmission so the bactrim protects him from contracting the virus." (Respondent 004, IDI)

Peer Influence and support

Peers and friends in the same study encouraged each other to continue adhering to CPT for their infants. This was reinforced by good health that the child enjoyed.

"When you are chatting, you are able to encourage one another, saying, "This child looks great. You shouldn't change. ...but there are other children who are not receiving bactrim. Their bodies do not look healthy; they are skinny. But on the

part of those who receive bactrim, they look fine. They are healthy." (Participant 005, FGD 2, Age 29, PE, Chikowi, Unemployed)

"I explained to my pastor…. "With this pregnancy you are seeing, I have been found with the infection, I am positive." He told me, "don't despair. We should be praying but also you shouldn't stop taking the treatment." Right now, whatever the little he finds, he shares it with me. Whether it is flour, he gives it to me, "Here is Likuni flour, use it for making porridge for the child." Because of that I thank my pastor for the support rendered to us." (Participant 008, FDG 3, Age 33, PE, Chikanda, Unemployed)

5.4.2.4 Deterrents from continuing with PMTCT interventions in children

Fear of stigma and discrimination

Study participants were asked to discuss some of the challenges that they encountered when administering CPT to the child as one of the PMTCT interventions in HIV exposed children. The first challenge was fear of discrimination by other family members as well as community members if they discovered the child was taking daily prophylaxis. This worry emerged because of the perceived and existing association between CPT and having HIV.

"… other people will ask you, "You always give this child bactrim, what is it for?" You see? So, it becomes difficult for you to answer because there is a group of people. …there are other people who begin to ridicule you behind your back, saying, "You shouldn't take her for her looks; she takes ARVs. 'Amamwatu' (she heavily takes ARVs)." That's the Chichewa that is there now, 'amamwa'. 'Amabwila' (vernacular term used to describe the act of chewing large quantities of powdery or crystal foods) daily. … when they have known about you, it will be the same talk. They will just wait for you to move away so they can discuss you. "Along this entire line [compound], all are sick. There is no one who is alive may be just one or two people." (Participant 002, FGD 1, Age 21, PE, Mikuyu, Unemployed).

Since mothers in this study were part of the large cohort study that followed up participants in their homes for study follow up procedures, some mothers experienced that their peers discriminated them against when the study staff visited them in their homes. Basing on this experience, they were afraid of being ridiculed if other people knew they were administering CPT to their children. One woman described her experience as follows:

"One day, this child got sick and three of us women went to a hospital. So, a certain man asked, "Are you going to the hospital?" The other man said, "This one who was diagnosed with the disease (HIV), her child is sick." So, I, the infected one, felt concerned in my heart." (Participant 005, FGD 1, Age 26, PE, Chidzalo, Unemployed)

Participants in a focus group discussion narrated that some community members considered the study as part of a satanic cult. They therefore discouraged the women from taking part in the study by stating that their children would die as demonstrated in the quote below.

"There are others who discourage us from this research in which we have enrolled our children. They say, "They are satanic. You will lose the children because of what you have enrolled in." When the project car visits you, they say, "What type of medical people are they who visit people in their homes?" "These doctors…what type of doctors are they who are just visiting [people] in their homes?" the first day this one picked us up, "Visiting people in their homes with expensive fuel this time around. They are satanic, you are going to sell out the children." (Participant 004, FGD 1, Age 38, PE, Magumba, Self-employed)

A child's intolerance of CPT

Some participants indicated that their children usually vomited the drugs during administration. They were therefore forced to re-administer the drugs but feared overdosing their children because they were not certain on the quantity that had been swallowed. They described this dilemma as follows:

"The challenge we encounter, some of the children vomit the drug when we give it to them. Nonetheless, we try all we can so that they take [the drug]. But that's the major challenge, vomiting the treatment." (Participant 9 FGD1, Male, 41year, Std7, Six Miles, Unemployed,)

"He does spit out everything. He can just spit a little bit and swallow the rest so fearing that I may overdose him, I do not re-administer." (Respondent 016, IDI)

There were opposing views on the steps to be taken after the child had vomited the medication as one woman suggested that re-administering the drugs was safe after 30 minutes from the previous administration of the drugs while another woman indicated that it was not advisable to re-administer drugs after the child vomited. However, some study participants indicated that they devised certain techniques to address the problem of child

vomiting the medication by either giving the child sugar or breast milk soon after administering the drugs to counteract its bitterness thereby preventing the vomiting.

> *"If it is the challenge of other children spitting out [the treatment], because of the bitterness of the treatment, to prevent the child from spitting out, we should coax him taking sugar. When the child takes the treatment, you give him sugar."* (Participant 002, FGD 1, Age 21, PE, Mikuyu, Unemployed)

> *"We entice the child when we want to give him the treatment; you take out the breast and offer it to him. Then he opens the mouth and you swiftly give him [the treatment] and then you give him the breast."* (Participant 5, FGD 1, Age 26, PE, Chidzalo, Unemployed)

Only one woman suspected that her child developed side effects after receiving CPT as she explained in this statement.

> *"…but one incident in particular; He had diarrhoea and he vomited and I came to the study clinic and was given medication, he improved and then later worsened."* (Respondent 017, IDI)

Forgetfulness

Although most of the participants mentioned that nothing would prevent them from ensuring that they adhere to CPT for their children, some cited a few reasons that encouraged non-adherence to CTP. The main reason given was forgetfulness on the part of the parent to administer CPT to the child. Participants stated that they sometimes forgot to give the medication to the child or carry the drugs with them when they were travelling. These incidents were said to happen infrequently.

> "*There are things that lead to failure, you might forget, the same forgetfulness we were talking about. You may have forgotten to give the child the treatment. This is one thing that also leads to failure to provide the treatment to a child…"* (Participant 004, FDG 2, Age 29, PE, Thom Allan, Unemployed)

Spousal disagreements, lack of food and shortage of drugs

Some of the issues mentioned that resulted into non-adherence to CPT included existing problems between partners in a family, lack of drugs, lack of food and lack of follow-up visits from health providers. In terms of relationship problems, the lack of understanding from a spouse and the absence of peace in the household were said to interfere with administration of CPT to the child. This has been illustrated in the quote below.

"... when there are disagreements and arguments between me and my spouse where my husband would want me to stop. Other than this I do not see anything else that can make me fail." (Respondent 004, IDI)

With reference to the lack of drugs, participants indicated that they failed to adhere to CPT treatment for their infants when their drugs run out without realizing or because when supply of fresh stock has not been done through home visits by study personnel as described by one woman.

"When the treatment has ran out it becomes a problem because those who visit and give us the treatment make a date with us, "we will be coming on such a day," but you find that they haven't come on that day. So, it becomes a problem because you wait thinking that the treatment will find you." (Participant 008, FDG 3, Age 33, PE, Chikanda, Unemployed)

Finally, some participants indicated that lack of food in the household was a reason why they sometimes failed to give CPT to their children. They perceived that giving a child medication on an empty stomach would make the child weak as described in the quotes below.

"If you don't have food, you fail to give the child the bactrim ... when the child reaches 6 months of age at which point the child needs to eat anything, but then you are found to have no food. Then you wonder, "Should I take the medication and give it to the child when I don't have food?" Then you just say, "Perhaps I should wait until the evening," because there is no food [laughs]..." (Participant 007 FDG 1, Age 22, PE, Magumba, Unemployed)

"It is really true because you can't give the treatment to a child before eating. The child might become frail... Also, when you go to the hospital, they advise you "Take this treatment after you have eaten. When you have eaten is when you should take it." So people draw a lesson from that." (Participant 011, FDG 1, Age 28, SE, Mpunga, Business)

Religious influence

On influence of religious and traditional beliefs, almost all participants stated that these did not influence their decisions or actions when giving treatment to their children. However, some pointed out that there were some religions that influenced them to avoid seeking treatment or defaulting on going treatment. One woman indicated that religion of

her spouse made her worry about continuing administering CPT to the child.

> *"My husband strongly believes that God exists so whenever I am giving bactrim he says that am torturing the child but I should leave him alone because God is in control and he is the one who gave us the child. It starts bothering me but I do not give up because I go to the hospital and follow the instructions given."* (Respondent 004, IDI)

5.4.2.5 Strategies for continued provision of CPT to their children

Reminders for CPT administration

The data shows that parents have a number of strategies that they use to remind themselves to administer CPT to their children. Their spouses and some household members including parents, siblings and older children reminded them to give CPT to their children. In addition to these, they used their daily routine activities as reminders for providing CPT to their child. These included: time for taking their ARVs, time for bathing the child, time for changing nappies, time for feeding the child and time when the sun rises. One woman described bathing and feeding of the child as a reminder for administration of CPT as stated below:

> *"What makes me remember…. is that every morning, the moment I bathe him and feed him porridge, I remember to administer bactrim. It is automatic, porridge is followed by bactrim."* (Respondent 014, IDI)

One mother stated that she used an alarm on her phone as a reminder to give CPT to the child. Below, another woman explained how timing for taking her ARV's helped her remember to give CPT to her child as well:

> *"I remember because when I am taking the drugs, when it is 6 o'clock, I know that the child should also take the treatment…. I remember to [give the drugs to the child] when I am taking my treatment."* (Participant 006, FDG 2, Age 24, PE, Chikanda, Unemployed)

Some women indicated that they conditioned their memory to remember administering CPT without any reminders. Also, some mothers kept drugs where they could easily see in their house and were reminded each time they saw the drugs. Here, a woman described how keeping CPT visible assisted her to remember administering the drugs to the child:

"My 'pillar' [reminder] is that I leave the drugs on a visible place so that I don't forget them." (Participant 003, FDG 2, Age 23, PE, Mpunga, Unemployed)

Carrying cotrimoxazole every time

A number of women indicated that they always carried the medication with them in case they travelled and this helped them ensure that the child adhered to treatment.

"Whenever I am going away, I put bactrim in his bag and I try my best to find time to give him the bactrim. I have never forgotten because whenever I am going away, I start packing the medication and his health passport before anything else." (Respondent 010, IDI)

5.4.2.6 Managing concomitant medications with CPT

On personal experiences on administration of CPT when the child was required to take other prescribed medication, participants indicated that they allowed the child to be on concurrent treatments. When asked what they did when a child got ill and required to be given other medications, respondents to this question showed that they continued administering CPT to their children even when they were required to take other medications. One participant demonstrated this in the quote below:

"I do not stop. I still give him say cough medicine when he has a cough or medication for fever if he has a temperature." (Respondent 003, IDI)

However, they understood that giving all of the different medications at once might be hazardous to the child. And therefore, they developed strategies to manage concurrent treatments for the child on CPT. Some of the women described how they managed giving different medications simultaneously to their child.

"I do not stop administering; I administer in the morning when feeding him porridge. If he is on another treatment, then I give him that treatment at 10 am." (Respondent 009, IDI)

"When I have more drugs to give the child ...I feel like the combination will make him weak, I alternate. I give him the other drugs at 6.00am and then Bactrim say at 8 am or 9 am to give space between the medications." (Respondent 010, IDI)

Data above shows the diversity in coping mechanisms in reference to the timing of concurrent medications to the child. Despite lack of standard guidelines to guide parents

on how to deal with such situations, most mothers still identified ways of ensuring the child took both treatments as one woman narrates.

"…. what I do now is to space bactrim and other drugs within a few hours." (Respondent 011, IDI)

However, some of the women made enquiries from the study clinic about the dangers of giving simultaneous treatment to the child before administering the medications as described in the quote below:

> *"I asked about this the last time I was admitted when he was taking niverapine and I was told that there was no problem and he could continue."* (Respondent 012, IDI)

The majority of mothers of HIV exposed children in this study explained that they continued providing CPT to their children even when the children were required to take other medications because they were motivated by the information and instructions provided by healthcare providers. This helped the women to be able to isolate the purpose of each of the medication given to the child and hence valued the need to ensure that the child took both or all medications.

> *"I already have the instructions from the doctors to continue administering. This is why I continue until they tell me to stop."* (Respondent 002, IDI)

Furthermore, women trusted that healthcare providers would not do anything to harm their children because they always checked the health passport book of the child before they provided a new prescription. One participant related this with her experience of being on ART where sometimes she had to take multiple drug regimens and felt this was supposed to be the same with children. She therefore did not have worries about giving CPT together with other medication as described below:

> *"There are no worries, when we fall sick, we are given different medications say Artemether Lumefantrine (AL) or others which we take simultaneously hence it is the same case with the child."* (Respondent 014, IDI)

5.4.2.7 The role of support systems in influencing uptake of PMTCT interventions in young children

Support systems mentioned in this study included support healthcare providers, family and the community (Table 5.4).

Support from healthcare providers

Most participants felt that the healthcare providers regularly supplied them with the drugs right in their homes during home visits for the CPT and malaria study consequently reducing the number of visits they would have to made to the hospitals to collect the medications. The constant interaction with these healthcare providers as they visited them was seen by most mothers as an opportunity to learn more on the medications. As such, the information gained assisted them to adhere to treatment in order to achieve its optimum benefits. Furthermore, the women felt supported with the reception they were given when they visited the study clinic either with a sick child or to collect more medications. Table 5.4 below includes women's narratives on how they perceived the support they received from healthcare providers, family and community.

Support from family members

Some participants had disclosed their HIV status to family members who they believed would support them. These included very close relatives mainly spouses, parents and siblings. However, some mothers said that they were cautious on informing some relatives about CPT considering high levels of stigma and discrimination as described by respondent 010, IDI (Table 5.4) who felt betrayed after her nephew disclosed her status to other members of the community.

Most participants valued the role of family relations in providing support in the administration of CPT. They narrated that support from close relatives is in the form of encouragement to continue providing CPT to their children, reminding them the time to give the child medication and helping in administering CPT to the child when the primary caregiver was away. Some indicated that they informed relatives about their participation in the malaria and cotrimoxazole study so that they were aware of what was happening. Informing relations was viewed as security for continued administration of CPT to the child in case the primary caregiver was incapacitated. However, one woman (Respondent 017, IDI) described that she informed relatives that she had joined the malaria and cotrimoxazole study to avoid suspicion that she had HIV and only disclosed her status to a relative who was also infected with HIV.

Support from the Community

Most women indicated that it was not proper to involve community members and religious institutions to provide social support to women who are providing CPT to their children. They stated that it was difficult to divulge confidential information to other people in the community for fear that they might use it against them. The excerpt for participant 008, FGD 3 in Table 5.4 describes why it was not advisable to inform community members about their HIV status. Most mothers indicated that they did not receive adequate support from community groups. Only two participants indicated to have obtained some kind of support from the two community-based organizations that implemented HIV-related activities in the district. This may explain why most of the participants felt that no external support from the community was required to support women in the administration of CPT. Here; one participant described why it is not advisable to inform community members about their HIV status:

> *"It is really essential to inform relatives but you should know which relative to inform and be certain, "If I inform this person, won't I hear the story at the [communal] tap?" You need to choose who to inform. So, when you notify them, you then explain to them and they keep privacy for you. But there are other relatives whom if you tell them, you will hear the story at the tap."* (Participant 001, FDG 2, Age 34, PE, Chiphola, Unemployed)

As a result of fearing negative consequences, some parents were forced to secretly administer CPT to their babies while fearing that they might be seen doing that by some members of the community. Some had to lie that the drugs were paracetamol as it is not associated with HIV. Fear of having their child bewitched by other people was another reason why some women did not want any involvement of the community members. Table 5.4 highlights what the women said about support from community members on administration of CPT to their infants

Table 5.4: Views of mothers of HIV exposed infants on the support systems for CPT provision

Women's views about support from healthcare providers	Women's views about support from family members	Women's views about support from other members of the community
"I am just thankful for a programme like this one, for our children's participation in the research about bactrim. We are just grateful [and ask you] not to stop here. Do the same even to our friends who are coming because we have followed the instructions that you give us. And we have seen that our children are growing up well with good health and not falling sick frequently because we have been following what you have been instructing us. So, we are asking you that this programme should proceed. It should not end here." (Participant 007, FDG 3, Age 36, SE, Six Miles, Unemployed)	*"… because the child lives with my younger sister when I go to work. I advise her, "You first cook porridge for the child. After you have cooked the porridge then feed the child with it. After feeding with the porridge, you should then take bactrim and give it to the child." This is happening because when I check the pills I find that they are decreasing."* (Participant 007, FDG 1, Age 22, PE, Magumba, Unemployed)	*"What I am afraid is that once people become aware, other people don't speak politely, 'You see that woman? She is on treatment.' In that way, you feel depressed by the mockery. So, to prevent being mocked, I told my child to keep a secret for me so that am not looked down and disheartened when I go out. When people see me, they should find me to be the same as they are* (Participant 008, FDG 3, Age 33, PE, Chikanda, Unemployed)
"It is fine because when we go to the hospital, the doctors welcome us with the usual courtesies, attends to the child and gives us medicine." (Respondent 010, IDI)	*"There are some relatives that I explained to; I told them that I joined the malaria study group from Zomba so they visit me and bring me medication for the child. They sometimes call me and I go there to get medicine that I administer to the child. Perhaps when they see the doctors they just suspect and do not ask, particularly my brother. But for the other relative I was explaining to, he is also on medication like me."* (Respondent 017, IDI)	*"No, they can't help us…religious people, community members/neighbors or our relatives. They can't manage because these drugs are very expensive. They can't afford to buy them. You the medical people are the ones who could help us. You should not get tired of us. Help us until the end of our lives."* (Participant 008, FDG 3, Age 33, PE, Chikanda, Unemployed)
"… I always give him away from the people, for example, in the house or in my bedroom. When they see me outside, I tell them that it is panado [Paracetamol] and the child needs it because he has fever or a cold but not many know because I have not spoken to them." (Participant 004, IDI)	*"I would say it has an advantage because life is too short. If I died, my child may be taken care of by relatives who may not know my status. They will not continue with bactrim and something bad may happen to the child."* (Respondent 016, IDI)	*I relate to them as normal as possible but they wonder why the doctors frequently visit me at home. I tell them that I joined malaria study but my child has not been found with malaria since. They then ask why the doctors come when the child has no malaria and I tell them that the doctors will stop when the child is diagnosed with malaria."* (Participant 007, IDI)
	If they know then it might be this other day where I had an argument with my nephew, that is when he started calling me	*"…they might see you giving the child the treatment. Then they will think that the child has an infection.*

	names and I believe people heard because it was in the evening and the calm of the night may have made us the only loud sound to be heard because in the morning some community members asked me what the commotion was all about." (Respondent 010, IDI)	*Then they could do their own things and the child could mysteriously become ill until the he dies."* (Participant 005, FDG 2, Age 29, PE, Chikowi, Unemployed)
	"You also need to keep privacy for yourself because, even if you inform your relatives, there are other relatives who do not know how to keep your confidentiality. They will inform another person, another person will inform another person. Then the story will have grown. When we get tested as we are doing, they scorn us. They feel that as you are taking the treatment, you are done." (Participant 002, FDG 2, Age 40, PE, Thabwani, Unemployed)	

5.4.2.8 Participants' worries about administering daily CPT

Most participants indicated that they did not have concerns about administering CPT to their children. However, the most cited worry raised by some was the burden of continuously giving the child medication and the possibility of inviting side effects from the medication. Here, mothers were worried about side effects of CPT to their babies.

> *"Usually it is feeling sorry for the child that he has to endure daily medication just because he was born from an infected mother but nothing big because I know the medication has been given by doctors who know their trade."* (Respondent 004, IDI)

> *"Since he is young and he is taking bactrim daily, I sometimes think that this might affect his mental capacity."* (Respondent 003, IDI)

The other worry raised by one woman was that the baby might sero-convert later on. The other one feared that health problems might emerge to the baby in the future once CPT was discontinued.

> *"Sometimes I just think about the pros and cons of medication, I think if I stop then problems will surface*." (Respondent 002, IDI)

5.4.3 Paediatric CPT uptake theory proposition and factors associated with CPT adherence

This study also aimed at providing an explanation of how HIV infected women's lived experiences, attitudes and life circumstances impact on their behaviours towards administering CPT to their HIV exposed but not infected children. This has been explained using application of some of the concepts from the Health Belief Model and Ecological theory of perception. Furthermore a diagrammatic presentation that follows, explains how different factors narrated by women influence adherence to CPT in HIV exposed children.

5.4.3.1 A theoretical explanation of paediatric CPT adherence

The theory being proposed combines aspects of both the Health Belief Model as well as the ecological theory of perception:

Understanding and acceptance of the present situation

The practice of adherence to long-term treatment in HIV disease in young children is influenced by both internal and external factors. It begins with the acceptance of the HIV

status by the mother and/or family during pregnancy and the value that the mother attaches to the life of her child coupled with her perceptions on severity of HIV, perceived susceptibility of the child to an HIV infection, perceived benefits of the interventions such as good health of the child, and perceived disincentives or barriers to uptake of the interventions like shortage of drugs.

Taking appropriate action-steps

In this phase, the understanding and acceptance of the situation prepares the mother to take appropriate actions to prevent HIV transmission to her newborn child. During pregnancy, the mother conforms to antenatal care, and Prevention of mother to child transmission of HIV (PMTCT) interventions and discloses her status to significant family members who render their support throughout. The mother remains cautious on how far she could disclose her status for fear of negative influence through rebuke, stigma and discrimination. After the child is born, the mother remains determined to protect her newborn child from contracting HIV. Although the child remains at a higher risk of getting infected with HIV during breastfeeding, the mother's self determination motivates her to take appropriate steps to ensure her child has access to preventive interventions. The mother sets out to obtain relevant information on available interventions and breaks boundaries of male domination in decision-making on health issues in order to access these interventions.

The prevailing environment

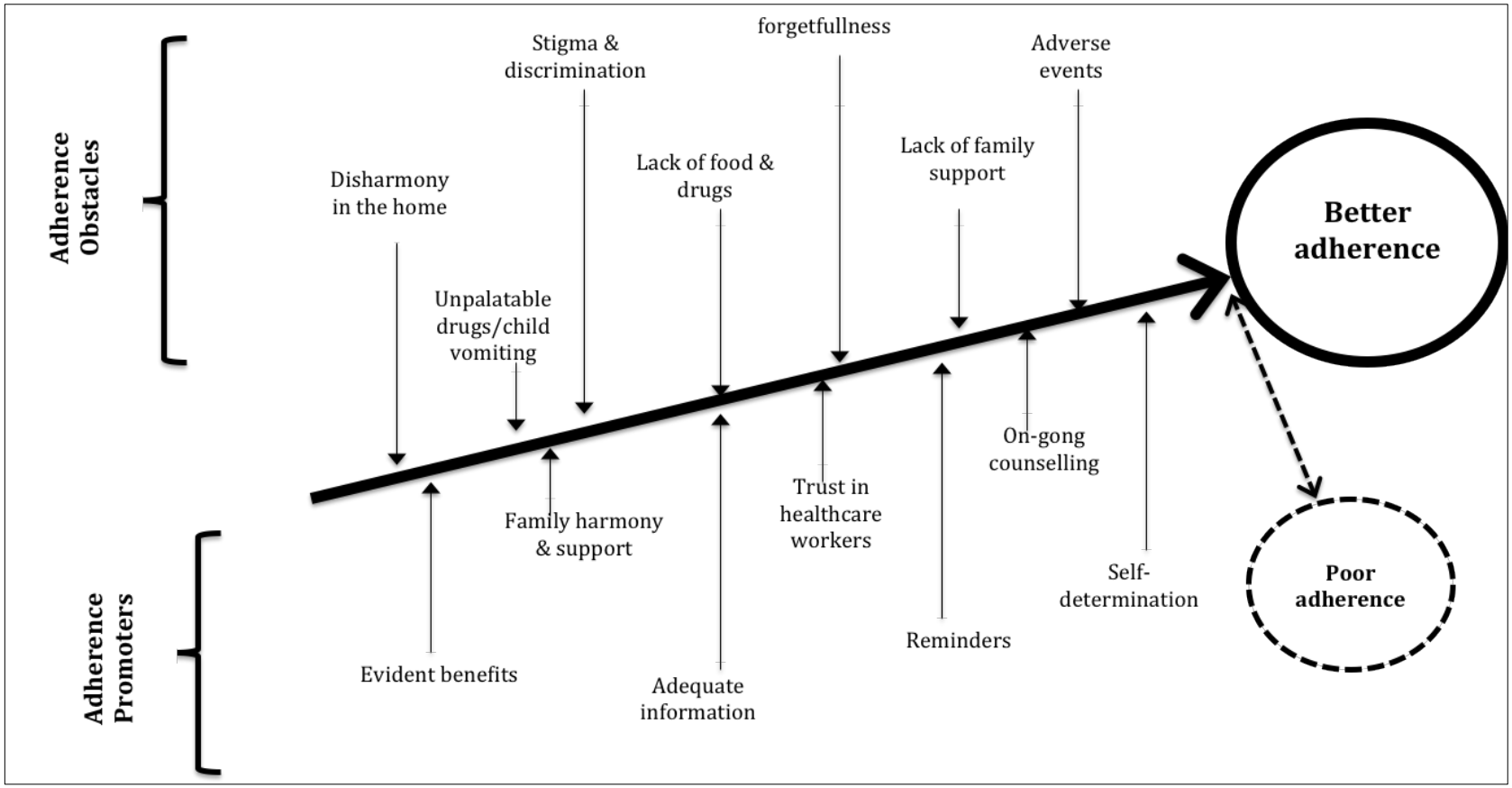
Family harmony, supportive family members and other forms of support, presence of reminders, adequate information, evident benefits from the intervention, trust in health care providers and rising above stigma and discrimination in HIV disease are some of the catalysts for determination to achieve better adherence to long-term treatments in young children (**Figure 5.1**). In contrast, lack of appropriate interventions like drugs and an inefficient health care system in general, lack of food, reminders and succumbing to stigma and discrimination are the factors fueling non-adherence to long-term interventions in children in resource-limited settings.

5.4.3.2 Factors associated with CPT adherence in HIV exposed children

Figure 5.1, illustrates how different factors work to influence adherence to CPT in HIV exposed children. Factors above the thick arrow leading to better adherence are obstacles to adherence. The presence of one or a combination of these factors deters these women from giving cotrimoxazole to their children. However, the arrows that point upwards

towards the thick arrow counteract this force and push the thick arrow along the double dotted arrow towards better adherence. The thick arrow moves downwards and upwards along the dotted double arrow between better and poor adherence depending on whether there are obstacles or promoters of adherence. For a sustained and better adherence, the thick arrow must remain in its current position. Improving and maintaining the ‘promoters of adherence’ below this arrow could achieve this.

Figure 5.1: Factors associated with adherence to cotrimoxazole prophylaxis in children



5.5 Discussion

This study sought to unveil the lived experiences of HIV infected women participating in a large cohort study on the impact of administering daily CPT to their HIV exposed children. It further aimed at establishing how these experiences impact on their behaviours in relation to continued administration of CPT. Finally; it isolated factors that influence paediatric CPT adherence.

The participation of women in the 'cohort study' had an influence on the way the decisions about giving CPT were made at the household level. As much as men being heads of households are mostly viewed as decision makers on most matters including health, women in this study rose above this phenomenon and took the right decisions to have their children access PMTCT interventions most especially CPT. In addition, being in the cohort study enabled these women to have access to information on CPT and develop strategies to ensure adherence among their children. The women depended on health workers for information about their children which empowered them to take appropriate decisions but also develop ways for compliance to interventions. Adequate information about the medication and on-going interaction between caregivers and the health care providers also reminded caregivers to administer cotrimoxazole to their children. Although few studies have shown that provider-patient-communication can improve the way communication is done during doctor-patient consultations and health and patient outcomes, there has been minimal and contradictory evidence on the effect of this communication on patient health care behaviour like adherence (Munro, 2007). Interestingly, this study shows that with good communication, women have access to adequate information about importance of the drug, its side effects and how it must be used. This information helps them to clear any misconceptions that might arise regarding the use of the drug and promotes trust between patients and providers. However, communication was not used in isolation to influence adherence because the women needed food, family support and the drugs themselves to ensure adherence. This concurs with a suggestion (Munro, 2007) that communication alone may not succeed in improving long-term adherence.

Only women participating in an on-going study were selected for the study due to time and financial constraints considering that if women from the community not participating in the on-going cohort study were to be recruited, it would have meant seeking ethical approvals and permissions from the local authorities all over again which would have required transportation from one place to the other and additional time. Those who were lost to follow up in the cohort study were not included in this study because they had either relocated to areas outside the study catchment area or had refused participation in the study. However, this must have been accounted for by how women were selected for this study. Inclusion of women at the beginning (2 months) of administering CPT would imply that some of the women who would eventually withdraw from participation during the course of the study participated in the qualitative study.

Secondly, this study sought to develop a theoretical explanation from the concepts that emerged from the narratives and the literature as an important ingredient to foster understanding of the experiences of parents/guardians of children on long-term treatment in chronic diseases in resource limited settings. The concepts emerging from the women's lived experiences show partial alignment to the ecological theory of perception and the Health Belief Model. The proposed theoretical explanation of CPT adherence therefore takes into account derivatives of the two theories. From an ecological perspective, the women themselves, their families, the communities in which they lived and the health care system were separate territories which related and influenced each other through social interaction and passing of information across the territories. This social interaction and information sharing played a role in influencing actions either positively or negatively. Depending on the nature of these processes, some might have been motivators such as a supportive family that helped someone to take a positive action and some might have been deterrents whose negative remarks and actions inhibited other people to take appropriate actions. The data in this study demonstrated that despite negative influences that might have arisen at any level, the determination of the individual to take a health-related action and the realisation that the recommended action would prevent any negative outcomes motivated the women to believe that they could successfully do something to prevent any negative health outcome. The women in this study used all available alternatives to ensure the child did not miss his

medications. This feature is a strong indicator of the Health Belief Model in which an individual feels that a negative health condition can be avoided by taking the appropriate health action.

Furthermore, the study has revealed many factors that influence CPT adherence in HIV exposed children in a semi-urban setting in southern Malawi (**Figure 5.1**). Lack of drugs at the health facility emerged as one of the reasons for non-adherence. This was attributed to inability by field workers to supply drugs to participants in their homes. In addition, informal conversations with most participants revealed that sharing of drugs between mothers and children due to stock outs in public health facilities (which were responsible for supplying CPT to the general population) contributed to lack of drugs for the child. This factor negatively affected adherence to CPT in children. The findings of a placebo-controlled study in Zambia, showed that despite high levels of adherence that were observed using objective as well as subjective adherence assessments, drops in adherence at certain time points were associated with running out of medications in between study visits (Walker, 2009). As cited by Shah A.C. this is one of the health care delivery related factors that influence adherence negatively (Shah, 2007). Issues of forgetfulness, inadequate information, travelling away from home and taking concomitant medications in the present study were also found to influence adherence negatively in the Zambian study (Walker, 2009). Gitta and others have also isolated travelling away from home and forgetfulness as some of the factors that influenced missing of cotrimoxazole prophylaxis in both HIV infected and HIV exposed children in Uganda (Gitta, 2007).

Although many studies on long-term adherence in paediatric HIV disease have focused on adherence to ART, the factors that influence adherence are similar to those influencing cotrimoxazole adherence. One explanation is that in both, children depend on caregivers for their medications hence any factors associated with HIV that affect the caregiver, would likely affect adherence for both ART and cotrimoxazole prophylaxis. In this study, HIV disclosure and accepting one's HIV status seemed to have positive influence on adherence in that women who accepted their status during pregnancy, took appropriate steps to prevent transmission of the virus to their children and would therefore adhere to cotrimoxazole for the benefit of their child irrespective of existing obstacles. Likewise, a study in Ethiopia in older

children, found that complete parental disclosure of HIV status to the child helped to motivate HIV infected children to adhere to their daily treatment regimes as they understood the infection and interpreted its implications thereby appreciated the importance of adherence (Biadgilign, 2008). Improvement in child's health status in Uganda fostered adherence to CPT among both infected and exposed children (Gitta, 2007). This was also the case in the present study where evident health benefits like sustained good health of the child motivated women to continue giving CPT to their children.

Fear of stigma and discrimination as a factor that deterred women from uptake of PMTCT interventions such as CPT in this study corroborates the findings of a study in India where women were not able to disclose their status to some of their family members for fear of isolation (Paranthaman, 2009). This negatively impacted on adherence as some women opted not to give medications to their children in the presence of other family members (Paranthaman, 2009). In the present study, the majority of women were skeptical about disclosing their status but also letting others know that their child was taking daily CPT for fear of rebuke and discrimination.

5.5.1 Possible limitations in interpretation of the study findings

Several factors must be considered when interpreting the findings. The study took place in Zomba, a semi urban district largely among women with low education levels and low social economic status hence the results presented cannot be applied to women in urban areas with higher education levels as well as socio-economic status. Views other than these would have been elicited if the study included women of higher educational levels, socio-economic status and those residing in urban areas. This is regarded as an important constraint because the interpretation of events surrounding administering CPT to HIV exposed children may be related to educational level, socio-economic status as well as residing in urban areas where health facilities are more closely distributed and sources of information are many. In addition, understanding of instructions, perceptions of illness and cultural positions may be different between urban and semi-urban dwellers.

Although educational level and age of participants for both FGDs and IDIs were presented, responses were not categorised by either age or educational level. This could have been done by categorising responses into primary and secondary education but also into age categories of for example <25 years and >25 years. This is an important limitation because adherence experiences may be different by age group as well as education category. Furthermore, the study population consisted of HIV infected women who were participating in a cohort study where they had access to information and their continued interaction with the study workers, might have influenced their behaviors regarding giving CPT to their children as well as their perception regarding PMTCT interventions in general. In addition their adherence to CPT might be related to the reasons for wanting to be in the PMTCT programme in the first place. These results therefore cannot be generalized to HIV infected women with HIV exposed but not infected children not participating in the study. Their being in the cohort study at the time of the interviews may limit generalization of the findings to women who withdrew from participation because their reasons for withdrawing might be related to uptake of CPT interventions.

Additionally, since most of these women (in the cohort study) were recruited from the PMTCT clinics, they were willing to have their children initiate and complete PMTCT and aware of the importance of adhering to CPT hence the responses provided in this study might be related to their initial intentions and not necessary asa result of the experiences during the study.

Although both IDIs and FGDs were conducted at a neutral venue away from the study clinic where these women regularly brought their children for clinical care, there is a possibility that the women knew what this study was looking for and this might have influenced their responses. In recognition of this, additional measures were followed to minimize such effects that included use of non-clinical staff to conduct the interviews.

The study focused more on the patient and the emerging concepts were largely patient related. More information on healthcare provider and health facility related factors would have been solicited if interviews were done with health care providers and pharmacy records were

checked respectively. Lastly, the researcher's medical background might have influenced the direction of the research to focus more on patient related perspectives to adherence ignoring health providers and health facilities.

5.5.2 Summary of Discussion

The discussion of this chapter highlights the experiences with administering CPT to HIV exposed children and how these affect household dynamics and coping strategies. It also presents the theoretical explanation of different aspects of adherence and factors that influence adherence to CPT in HIV exposed children.

CHAPTER 6 : GENERAL DISCUSSION, RECOMMENDATIONS AND CONCLUSIONS

6.1 Introduction

6.1.1 Summary of the findings

The studies in this thesis show a more than 60% reduction in the incidence of uncomplicated malaria associated with the use of CPT with no evidence of increase in uncomplicated malaria after CPT was stopped. HIV infected women's participation in the cohort study empowered them to make better decisions for the health of their children and develop appropriate strategies for compliance. These findings are based on the three studies included in this thesis. A systematic review and a meta-analysis (chapter 3) reviewed the effect of cotrimoxazole prophylaxis on malaria and mortality in children living in sub-Saharan Africa, and showed a 63% reduction in the risk of clinical malaria and 43% in all-cause mortality. Our subsequent prospective cohort study in Malawi showed a 65% reduction in the incidence of uncomplicated malaria (chapter four). There was no evidence of increase in the incidence of uncomplicated malaria after CPT was stopped (i.e. no rebound effect). Finally, a qualitative study explored the experiences of HIV infected mothers administering daily CPT to their HIV_{ex} children enrolled in the cohort study (chapter five). HIV infected women with HIV_{ex} but not infected children were motivated to continue administering CPT to their children because of the evident health benefits in their children.

6.1.1.1 CPT is highly effective in preventing uncomplicated malaria, severe malaria and other comorbidities in children

The 63% and 65% reduction in malaria incidence obtained from the meta-analysis and the cohort study respectively, is an indication that CPT provides effective chemo-prophylactic effect against malaria. Although highly heterogeneous, the findings of the review have important clinical implications. The review shows that CPT has a strong impact on preventing malaria despite widespread resistance to it (chapter 3). This has been supported by the findings of the cohort study (chapter 4) evaluating the effect of CPT on the incidence of uncomplicated and severe malaria. The overall incidence of uncomplicated malaria appeared higher in year 1 than in year 2 but multiple regression analysis on the effect of group showed a 65% lower risk in HIV_{ex} children in year 1 compared to their HIV_{un} counterparts consistent

with previous findings of studies evaluating the effectiveness of CPT on malaria prevention (Sandison, 2011).

6.1.1.2 Stopping CPT in HIV exposed children does not increase the risk of the incidence of uncomplicated malaria in HIV exposed children (malaria rebound effect)

In contrast to previous observations showing an increase in the incidence of malaria after stopping malaria chemoprophylaxis (Greenwood et al., 1995), there was no evidence of malaria rebound effects in this study as the incidence was similar between the HIV_{ex} and HIV_{un} group in year 2 after CPT had been stopped. This is one of the first studies to investigate malaria rebound after stopping CPT. However, this finding represents only 60% of the follow up time as the study is still on-going but significant changes after completion of the study are unlikely considering that a more recent RCT in Uganda did not also find any malaria rebound effects when CPT was extended for four years (Homsy, 2014).

6.1.1.3 Evidence of increase in the incidence of severe malaria after stopping CPT in the HIV exposed group

Surprisingly, an increase in the incidence of severe malaria was observed after stopping CPT in the HIV_{ex} group. Although not statistically significant and not expected considering the lack of rebound with uncomplicated malaria, it is not necessarily inconsistent with existing epidemiological data (Mockenhaupt, 2007). The decline in susceptibility to malaria infection during CPT may have resulted in enhanced risk of severe disease when the children were first exposed to malaria infection in year 2 after CPT had been stopped. Such a scenario is suggested to affect the rate of the disease adversely by delaying the average of first infection thereby reducing the enhancement of the immunity that may be necessary for the maintenance of immunity to severe malaria (Gupta, 1999). Moreover, the exposure to HIV in utero and during the breastfeeding period might have affected development of the infant's immune system resulting in immunological abnormalities and increased susceptibility to morbid events and hospitalisations as evidenced by a lack of significant decrease in all-cause sick visits and increase in the rate of hospital admissions in HIV_{ex} children after CPT was stopped.

6.1.1.4 Stopping CPT does not show real evidence on impact on all-cause mortality

Although a meta-analysis on the effect of CPT on mortality in children was not possible due to small number of studies, an RCT in the systematic review demonstrated substantial reductions in mortality with the use of CPT (chapter 3). Surprisingly, the observational study (chapter 4) was not able to show protective effect of CPT on all-cause mortality. Although year 2 estimates were not statistically significant, they have important clinical implications and worth consideration in the clinical management of these children.

6.1.1.5 Women's perceptions on administering CPT to their HIV exposed children

The qualitative study revealed the impact of participating in the CPT programme and/or a research study on household parameters such as decision making as well as social support regarding administering daily CPT to HIV exposed children. In addition, both deterring and facilitating factors for continuing to administer CPT in HIV exposed children in southern Malawi were highlighted in this study. Although there is lack of evidence on the influence of home study follow-ups on uptake of long-term interventions for HIV exposed children, this study shows that the household visits acted as reminders for continued administration of CPT. In addition, the information HIV infected women received through the participation of their HIV exposed children in the cohort study empowered them to make appropriate decisions about the health of their children and develop strategies that they found helpful for the continued administration of CPT to their children. The improved health outcomes of their children further motivated them to continue with the available interventions for their children.

6.1.1.6 Theoretical perspective of women's motivation to continue administering CPT to their HIV exposed children

The proposed theory outlines the interrelatedness of several processes that eventually influence paediatric CPT adherence in HIV_{ex} children. The key message is the influence of these processes on paediatric medication adherence. The women present a rare character where they rose above the boundaries of male-dominated household decision making on the health of their children in situations where the male partner seemed resistant to seek care for their children. The proposed theory amalgamates the experiences these women go through in their daily lives to present an understanding of how such processes can influence adherence to long term HIV associated medications such as CPT in HIV_{ex} children.

6.2 Recommendations

6.2.1 General Recommendations

As the increase in the number of HIV infected pregnant women having access to improved PMTCT interventions results in fewer new HIV infections in infants born to these women, the need for appropriate services and improved delivery of the same for HIV exposed children cannot be ignored. The increase in the number of HIV exposed children is a call to strengthen the capacity of health facilities to provide quality and long term services for this population while taking into consideration the effects of such services. Since HIV_{ex} children are more susceptible to childhood illnesses compared to HIV_{un} children due to their nature of being HIV exposed (Slogrove, 2010, Hygino, 2008, Mussi-Pinhata, 2007), overall child survival should continue to be a priority. One of the key interventions that require special attention is the use of CPT for the prevention of HIV opportunistic infections. In addition, gaining a deeper understanding of the impact of this intervention on the children and their families is crucial to providing better care. Surveillance for adverse events in these infants as well as more robust systems to capture consequences resulting from interruption of these interventions are a priority to fully understand the outcomes of this intervention and thereby develop effective strategies to prevent any health risks resulting from such. This is particularly important in poor resource settings where parasitic infections, malnutrition and other comorbidities are more common and in which monitoring capacity is limited. Table 6.1 contains a list of summarized recommendations.

Table 6.1: Key Messages and summary of recommendations

- CPT remains an effective intervention for HIV exposed children for both general morbidity as well as malaria and is an important programme that needs to be strengthened and scaled up through:
    - Maintenance of CPT stocks in all health facilities,
    - Continued counselling for HIV infected women with young children to promote uptake,
    - Involvement of spouses and significant family members for social support.
- Stopping CPT at 12 months after cessation of breastfeeding and confirmation of a negative

HIV test is safe, as it does not increase the risk of the incidence of uncomplicated malaria as previously postulated implying that HIV exposed can stop CPT without increasing their risk of malaria.

- Participation in PMTCT programmes empowers the women to develop useful strategies that promote positive heath outcomes in their children. The following are recommended:
    - Strengthening of available support groups of HIV infected women to promote information sharing and peer motivation

      On-going counselling to promote positive health behaviour

6.2.2 Future Research

The non-significant evidence of a rise in the incidence of uncomplicated malaria and other outcomes observed in year 2 in the cohort study raises a number of questions such as whether the cessation of CPT is a contributing factor for this increase or is it a consequence of immunological challenges associated with exposure to HIV in utero as well as during breastfeeding. Since the present study was not designed to investigate these factors, future studies should focus on assessing whether long term and sustained use of CPT interrupts acquisition of natural immunity to malaria and whether duration of breastfeeding and nutritional status have any role in the findings observed in this study.

The systematic review and meta-analysis presented in this thesis are the first to assess the effect of cotrimoxazole on the prevention of malaria in children in sub-Saharan Africa. Since it mainly focused on children, future research should investigate whether the effect is the same in adults and HIV infected pregnant women. More evidence on HIV uninfected populations is needed in order to answer the question whether cotrimoxazole should become an option in the control of malaria among the general population in sub-Saharan Africa.

More field research is required to test the proposed theoretical explanation of CPT adherence in HIV exposed children in order to prove it scientifically. More research on measuring adherence in this population must also involve healthcare providers and review of pharmacy records in order to understand concepts that affect adherence from these perspectives.

Additionally, quantitative research methods would help establish associations and isolate the factors that are significantly related to adherence.

6.3 Limitations

The general limitations for this project included the use of restricted dataset, which included all of the first year follow-up but only about 60% of the second year follow-up, which was still ongoing by the time the thesis had to be submitted. It is unknown at this point whether this will have implications for the interpretation of the findings for this study. For example, if the effect estimates themselves remain similar, the potential increase in severe malaria observed in this preliminary analysis may become statistically significant when the full study is completed. In addition, the limited funding that was available for the study limited inclusion of other groups of women in the qualitative study like those who did not participate in the cohort study and those who were lost to follow up thereby limiting generalization of the study findings.

6.4 Conclusions

This being the first known study to review the malaria protective efficacy of CPT in children in SSA, investigate malaria rebound effects following cessation of CPT in HIV_{ex} children and also the first one to explore experiences of HIV infected mothers administering CPT to their HIV uninfected children, it contributes a large body of knowledge to the limited data on the pooled effect of CPT on malaria but also provides cutting edge information on the effect of stopping CPT in HIV exposed children after cessation of breastfeeding and determination of their HIV status. Furthermore, it provides a narrative of the experiences of administering a long-term treatment to children who are presumably "healthy". This knowledge gap could be a possible reason for unavailability of guidelines in Malawi and elsewhere on the management of these children when they are taking CPT and after they have stopped. Given this reality, the findings of this study may contribute to the debate on the possible interventions suitable for these children. Despite the highly heterogenous estimates observed from the meta-analysis, the findings obtained in both studies (meta-analysis and cohort studies) have important clinical implications. Finally, HIV infected women benefit from

regular contacts with health professionals from which they obtain information that guides their decisions about the health of their children.

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Appendices

Appendix 1: The PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

Appendix 2: Data Extraction form for Systematic review and meta-analysis

In HIV infected and exposed children, does cotrimoxazole prophylaxis reduce malaria incidence and mortality compared to children not receiving cotrimoxazole?: A Systematic Review and Meta-Analysis

Article Title:	
First Author:	Data Extracted by:
Journal:	Date Completed:
Year of Publication:	Calendar time study was conducted:
Author contacted: ☐ Yes (date) _____ ☐ No ☐ Responded (date)_____ Email:	Study Design: Observational Study ☐ Randomized Controlled Trial ☐ Country:
Final Status: ☐ Included ☐ Excluded (reasons):	

STUDY CHARACTERISTICS

Characteristic	**Response**	
	Yes	**No**
Type of Publication		
Journal Paper	☐	☐
Dissertation	☐	☐
Unpublished paper	☐	☐
Other	☐	☐
Study Setting		
Urban	☐	☐
Rural	☐	☐
Not Able to tell	☐	☐
Institution	**Please tick**	**Please tick**
Teaching Hospital	☐	☐
Health Centre	☐	☐
PMTCT Program	☐	☐
Referral Hospital	☐	☐
District/provincial hospital	☐	☐
Research Institution	☐	☐
Community	☐	☐

Other Specify	_____	_____
No of participants		
	Cotrimoxazole Group	**No cotrimoxazole group**
	(insert number here) ☐ Not able to tell	*(insert number here)* ☐ Not able to tell
Sex Males Females Not Able to tell	 ☐☐☐ ☐☐☐ ☐	 ☐☐☐ ☐☐☐ ☐
Age Age Median Age Mean Age Age Range IQR Not Able to tell	 _____ _____ _____ _____ _____ ☐	 _____ _____ _____ _____ _____ ☐
HIV Status HIV Infected HIV exposed HIV Negative Not Able to tell	 ☐ ☐ ☐ ☐	 ☐ ☐ ☐ ☐
Follow Up Period		
Overall Mean Median Range IQR Not Able to tell	_____ _____ _____ _____ _____ ☐	_____ _____ _____ _____ _____ ☐
Treatment dosage and duration	**Cotrimoxazole:**	**Placebo/comparison treatment:**
Other malaria interventions	☐ Insecticide Bed Nets ☐ Impregnated curtains ☐ Intermittent preventive treatment in infants (IPTi) ☐ Indoor Residual Spraying (IRS) ☐ Other chemoprophylaxis ☐ Not able to tell	☐ Insecticide Bed Nets ☐ Impregnated curtains ☐ Intermittent preventive treatment in infants (IPTi) ☐ Indoor Residual Spraying (IRS) ☐ Other chemoprophylaxis ☐ Not able to tell
Use of Antiretroviral Treatment	☐Yes ☐ No ☐ Not able to tell	☐Yes ☐ No ☐ Not able to tell

Study Outcomes	**Cotrimoxazole Group**	**No Cotrimoxazole**
Malaria		
Number of Events Overall Incidence Unadjusted IRR (95% CI) Adjusted IRR (95% CI)	_____ _____ _____	_____ _____ _____
Mortality		
Number of Events Overall Incidence Unadjusted HR (95% CI) Adjusted HR (95% CI) No adjusted analysis performed	_____ _____ _____ _____ ☐	_____ _____ _____ _____ ☐
Confounding factors		
	(tick all that apply) ☐ age ☐ sex ☐ HIV status ☐ Breastfeeding ☐ Living in urban vs. rural areas ☐ use of mosquito net ☐ use of other antimalarial chemoprophylaxis ☐Previous episode of malaria ☐ other confounders *List:* ☐ no adjusted analyses performed	*(tick all that apply)* ☐ age ☐ sex ☐ HIV status ☐ Breastfeeding ☐ Living in urban vs. rural areas ☐ use of mosquito net ☐ use of other antimalarial chemoprophylaxis ☐Previous episode of malaria ☐ other confounders *List:* ☐ no adjusted analyses performed
Prevalence of dhps and dhfr gene mutations	Mutant Gene: _____ _____ _____ _____ _____ _____ ☐ Not reported	Prevalence _____ _____ _____ _____ _____ _____ ☐ Not reported

Appendix 3: Enrollment Case Report Form (Visit 1)

Malaria rebound in HIV exposed children after stopping cotrimoxazole prophylaxis

Form Completed by ☐☐☐ *(Initials)*
Client Initials ☐☐☐ *(Initials)*
Date Completed ☐☐ / ☐☐ / ☐☐ *(dd/mm/yy)*
Type of Client ☐ *1=HIV exposed, 2=non-HIV exposed*

LAB INVESTIGATIONS (before history taking, collect blood samples and send for processing)

Finger prick for malaria smear ☐*1=Yes, 2=No* Filter paper ☐*1=Yes, 2=No, Hb* ☐*1=Yes, 2=No*

DEMOGRAPHIC DATA

1. Date of birth ☐☐ / ☐☐ / ☐☐*(dd/mm/yy)* ***(DO NOT LEAVE BLANK)***
2. Is birth weight available from the health passport? ☐*1=Yes, 2=No*
   If available, record ☐☐.☐ kgs
3. Sex ☐ *1=Male 2=Female*
4. Ethnic origin ☐ 1=*lomwe*, 2= *Yao, 3= Chewa, 4=Sena, 5=Mang'anja,6=Tumbuka,7= Ngoni ,*
   *8=Unknown, 9= other specify*_____
5. Religion ☐ 1=*Catholic, 2= Moslem, 3=Prot Major, 4=Prot Adventist, 5= Pentecostal 6=unknown, 7=other, specify*
6. Age of mother (years) ☐☐
   Is it Estimated or Actual ☐ *1= Estimated, 2= Actual*
7. Education:Mother ☐ *1=No formal Education*, 2=*primary, go to primary*, 3=*secondary, go to sec 4= tertiary*
   If Primary ☐ *1= Able to read and write, 2= Not able to read and write*
   If Secondary ☐ *1=Form 1, 2=Form 2, 3=Form 3, 4=Form 4*
8. Job Mother ☐ *1=employed, 2=not not employed*
   If employed specify: ☐*1=Yes, 2=No*, self employed ☐*1=Yes, 2=No*, white collar job ☐*1=Yes, 2=No*, Farming ☐*1=Yes , 2=No*, part time piece works ☐*1=Yes, 2=No*, Driver ☐*1=Yes, 2=No*, Domestic ☐*1=Yes, 2=No*, Other job specify_____
9. Marital Status ☐ *1= married, 2=widowed, 3=Divorced, 4=Separated, 5=Not married, **If not married, SKIP TO QUESTION 12***
   If married, ☐ *1= Partner alive, 2=Cohabiting with partner,*
10. Job Father ☐ *1=employed, 2=not not employed*
    If yes, employed specify*:* self employed ☐*1=Yes, 20=No*, white collar job ☐ *1=Yes, 2=No*, Farming ☐ *1=Yes, 2=No*, part time piece works ☐*1=Yes, 2=No, Driver* ☐ *1=Yes, 2=No* Domestic, Other job specified_____
11. Education Father: ☐*1=No formal Education* 2=*primary*, ***go to primary***, *3= secondary,*

go to sec , 4=tertiary

If Primary ☐ *1= Able to read and write, 2= Not able to read and write*

If Secondary ☐ *1=Form 1, 2=Form 2, 3=Form 3, 4=Form 4*

12. Does the family have the following? Cattle ☐ *1=Yes, 2=No*, bicycle ☐ *1=Yes, 2=No*, TV ☐*1=Yes, 2=No*, Radio/CD ☐*1=Yes, 2=No*, Land ☐ *1=Yes, 2=No*, car/motorbike ☐ *1=Yes, 2=No*

13. Number of siblings: ☐☐ Alive ☐☐ Dead *(only same mother and father)*

HOUSEHOLD CHARACTERISTICS

14. Use of Electricity ☐*1=Yes, 2= No*

(For questions 15 & 16, tick all that apply)

15. Water Source

tap ☐*1=Yes, 2=No*

Borehole ☐*1=Yes, 2=No*

Stream ☐*1=Yes, 2=No*

Well ☐*1=Yes, 2=No*

*Other specify*_____

16. Dwelling roof type

Iron sheets ☐*1=Yes, 2=No*

Grass thatched ☐*1=Yes, 2=No*

Tiles ☐*1=Yes, 2=No*

Not known ☐ *1=Yes, 2=No*

MOTHER'SHEALTH STATUS

17. Is the mother on any long term treatment ☐ ***1=Yes, 2= No*** *if no, go to Q19*

If yes (tick ALL that apply)

ART ☐ *1=Yes, 2=No* TB treatment ☐ *1=Yes, 2=No* Cotrimoxazole prophylaxis ☐*1=Yes, 2=No* Vincristine ☐*1=Yes, 2=No* Antihypertensives ☐ *1=Yes, 2=No* ant asthmatics ☐*1=Yes, 2=No*, ant-epileptics ☐, *1=Yes, 2=No* ant fungal ☐ ,*1=Yes, 2=No* diabetes drugs ☐ *1=Yes, 2=No* Other Specify _____

(For questions 18 & 19, check in health passport or mothers HIV care records)

18. Is the CD4 Count of mother available ☐ 1=*Available, 2=not available*

If available, record ☐☐☐ */mm*^{3} *Date* ☐☐/☐☐/☐☐ *(dd/mm/yy)*

19. Is the Viral Load of Mother available ☐ 1=*Available, 2=not available*

If the Viral Load available is it detectable? ☐ *1= Detectable, 2=Not Detectable*

If detectable, record ☐☐☐☐☐☐☐ copies/*ml Date* ☐☐/☐☐/☐☐ (*dd/mm/yy)*

MALARIA CONTROL MEASURES

20. How many mosquito nets are in use in the home ☐☐ *1=0, 2=≥1,* **if 0, SKIP TO Q25**

21. Are the nets treated with insecticide ☐ *1=yes, 2=no*

22. When did you last treat the nets ☐ *1= Last month*, 2=Two months, *3=6 months, 4=Not Remember*.

23. How often do you treat mosquito nets ☐ *1= never, 2=0nce a year, 3=once in 6 months, 4=not known*.
24. Did child sleep under a mosquito net last night? ☐ *1=Yes, 2=No* ***(No, go to Q25)***
If yes; is net treated with insecticide? ☐ *1=Yes, 2=No, 3=Not known*
If no, specify reason *(tick **ALL** that apply)*
Forgot ☐*1=Yes, 2=No,* Allergic to ITN ☐*1=Yes, 2=No,* did not sleep at home ☐ *1=Yes, 2=No,* was used by others ☐ *1=Yes, 2=No***,** other specify _____
25. Do you use any of the following malaria control measures (tick **ALL** that apply)
Indoor Residual Spraying (IRS) ☐ *1=Yes, 2=No*
Coils ☐ *1=Yes, 2=No*
Body repellents ☐ *1=Yes, 2=No*
Sprays e.g. Doom ☐ *1=Yes, 2=No*
Traditional medication ☐ *1=Yes, 2=No*
None ☐ *1=Yes, 2=No*
Others specify _____
26. When you suspect that your child has malaria, what action do you take*? (Tick **ALL** that apply)*
Go to the hospital ☐*1=Yes, 2=No,* Buy medication from pharmacy/shops ☐*1=Yes, 2=No,* Do tepid sponging ☐*1=Yes, 2=No,* Traditional medication ☐*1=Yes, 2=No,*

PREVIOUS MEDICAL HISTORY

(Use child's health passport if available)
27. Has child suffered any febrile illness before? ☐*1=Yes, 2=No*
28. Has child been admitted before? ☐ *1=Yes, 2=No, IF **NO, SKIP TO QUESTION 29***
If yes, How many times has child been admitted? ☐☐ Time/s (indicate number in box)
Please give details of the last two admissions below:
Previous Admissions 1 ☐*1=Yes, 2=No* *If 'yes' Specify date* ☐☐ / ☐☐ / ☐☐ *(dd/mm/yy) If 'yes' Specify diagnosis* _____
Previous Admissions 2 ☐1=*Yes, 2=No If 'yes' Specify date:* ☐☐ / ☐☐ / ☐☐ *(dd/mm/yy) If 'yes' Specify diagnosis* _____
29. Is child currently on Antibiotics ☐*Yes, 2= No, IF **NO, SKIP TO QUESTION 30***

If yes specify name:	**start date**	**Duration**
Amoxycillin	☐☐ / ☐☐ / ☐☐ *(dd/mm/yy)*	☐☐*days*
Erythromycin	☐☐ / ☐☐ / ☐☐ *(dd/mm/yy)*	☐☐*days*
Augmentin	☐☐ / ☐☐ / ☐☐ *(dd/mm/yy)*	☐☐*days*
Cholramphenicol	☐☐ / ☐☐ / ☐☐ *(dd/mm/yy)*	☐☐*days*
Ceftriaxone	☐☐ / ☐☐ / ☐☐ *(dd/mm/yy)*	☐☐*days*
Gentamycin	☐☐ / ☐☐ / ☐☐ *(dd/mm/yy)*	☐☐*days*
Benzyl Penicillin	☐☐ / ☐☐ / ☐☐ *(dd/mm/yy)*	☐☐*days*

Other Specify _____
30. Is the child currently on malaria treatment? ☐ *1=yes, 2=no,* **IF NO, SKIP TO Section G**

If yes, specify type:	*Date prescribed*	*duration in days*
Artemether Lumafantrine (AL)	☐☐ / ☐☐ / ☐☐ *(dd/mm/yy)*	☐☐*days*

Sulphadoxine Pyrimethamine(SP) ☐☐ / ☐☐ / ☐☐ *(dd/mm/yy)* ☐☐*days*
Quinine Sulphate ☐☐ / ☐☐ / ☐☐ *(dd/mm/yy)* ☐☐*days*
Traditional medication ☐☐ / ☐☐ / ☐☐ *(dd/mm/yy)* ☐☐*days*
Other specify_____ ___

CURRENT MEDICAL STATUS

31. Is your child having any complaints? **IF NO, SKIP TO QUESTION 32**

Fever	☐*1= Yes, 2=No.*	*If 'yes', duration* ☐☐ *days*
Cough	☐ *1=Yes 2=No.*	*If 'yes', duration* ☐☐ days
Vomit	☐ *1=Yes, 2= No.*	*If 'yes', duration* ☐☐ days
Diarrhoea	☐ *1=Yes, 2=No.*	*If 'yes', duration* ☐☐ days
Rash	☐ *1=Yes 2=No*	*If 'yes', duration* ☐☐ *days*

Other specify _____

32. Is child having any of the following? IF NO, SKIP TO QUESTION 33

Bloody stool	☐*1=Yes, 2=No*
Bloody urine	☐ *1=Yes, 2=No*
Jaundice history	☐ *1=Yes, 2=No*
Respiratory distress	☐ *1=Yes, 2=No*
Coma	☐ *1=Yes, 2=No*
Convulsing	☐ *1=Yes, 2=No*

CLINICAL EXAMINATION

33. Anthropometric measurements

Weight ☐☐.☐ *kg* length ☐☐.☐ *cm* MUAC ☐☐.☐ *cm*

34. Vital signs

Pulse rate ☐☐☐ *beats/min*
Temperature ☐☐.☐ *ºC*
Respiratory rate ☐☐☐ */min*

35. Other Signs

a) Chest signs ☐ 1=*Yes, 2= No (**If no, go to b**)*
If yes, specify (tick **ALL** that apply)
Chest recessions ☐*1=Yes , 2=No*
Crepitations ☐ *1=Yes, 2=No*
Tachypnea ☐ *1=Yes, 2=No*
Hyperinflation ☐*1=Yes, 2=No*
Wheezing ☐ *1=Yes, 2=No*
b) Oedema ☐ *1=Yes, 2= No.* .
c) Lymphadenopathy ☐ *1=yes, 2=no, If no, go to (d)*
If yes, ☐ 1=*Regional, 2=General*
d) Pallor: Conjunctival ☐ *1=present*, 2= absent, ***if no, go to (e)***
If Conjunctival= *present*, ☐ *1=Mild/moderate, 2= Severe*
e) Dehydration ☐ *1=yes, 2= no, if no, go to (f)*
If yes ☐ *1=Mild, 2= Moderate, 3= Severe,*

f) Spleen ☐☐ *cm*
g) Liver ☐☐ *cm*
h) ENT/mouth abnormal ☐ *1=Yes, 2= No*. ***If yes, specify :*** Thrush☐ *1=yes, 2= No*
sores☐ 1=*yes, 2=No* ***If other, please specify*** _____
i) Jaundice? ☐ *1=Yes, 2=No*

LAB INVESTIGATIONS : ***Please complete visit 1 laboratory form***
Hb ☐☐.☐ g/dl
Malaria slide ☐ *1=positive, 2= negative*
If positive, severity ☐ *1=1+, 2=2+, 3=3+, 4=4+*

J. DIAGNOSIS

*35) **a)*** Presenting diagnosis 1 ☐☐☐☐ *code and Specify* ___
b) Presenting diagnosis 2 ☐☐☐☐ *code and Specify* ___

K. TREATMENT

Anti-malarials given? ☐ *1=Yes, 2=No*
Antibiotics given? ☐ *1=Yes, 2=No*
CPT ☐ *1=Yes, 2=No*
Other drugs given? ☐ *1=Yes, 2=No*

Drug details of anti-malarials, antibiotics and other drugs given

Drug	**Dose (mgs/tablets) & frequency**	**Duration (days)**

Appendix 4: Community Follow up Case Report Forms (Visits 2-11)

Malaria rebound in HIV exposed children after stopping cotrimoxazole prophylaxis

Form Completed by ☐☐☐ *(Initials)*
Date Form Completed ☐☐ / ☐☐ / ☐☐ *(dd/mm/yy)*
Client Initials ☐☐☐ *(Initials)*
Type of Visit ☐ 1=*Visit 2,2= Visit 3,3=Visit 4,4=Visit 5, 5=Visit 7, 6=Visit 8, 7=Visit 9, 8=Visit 10, Visit 11.*
Type of Client ☐ *1=HIV exposed, 2=non-HIV exposed*

If the subject is HIV exposed go to Section A, if non-HIV exposed go to SECTION B

SECTION A: HIV Exposed

MOTHER'S HEALTH STATUS

1. Is the mother alive? ☐ *1=Yes, 2=No* If yes *GO TO QUESTION 2*
   If No, Did death occur since last visit? ☐ *1=Yes, 2=No*
   If yes, indicate date: ☐☐ / ☐☐/☐☐ and SKIP TO QUESTION 4
2. Is the mother on any long-term treatment? ☐ *1=Yes, 2=No if no, SKIP TO* QUESTION
3. If yes *(tick ALL that apply)*
   ART ☐*1=Yes, 2=No,* TB treatment ☐*1=Yes, 2=No,* Cotrimoxazole prophylaxis ☐ *1=yes, 2=No,* Vincristine ☐*1=Yes, 2=No,* Antihypertensives ☐*1=Yes, 2=No,* ant asthmatics ☐*1=Yes, 2=No,* ant-epileptics ☐*1=Yes, 2=No,* ant fungals ☐*1=Yes, 2=No* diabetes drugs ☐*1=Yes, 2=No,* Other Specify _____

MALARIA CONTROL MEASURES

3. How many mosquito nets are in the home since last visit ☐☐ *1=0, 2=≥1.* If answer is 0, **GO TO Q5**
4. Did child sleep under a mosquito net last night? ☐ *1=Yes, 2=no (No, go to Q4b)*
   If yes; is net treated with insecticide? ☐ *1=Yes, 2=No, 3=Not known*
   If no, specify reason *(tick **ALL** that applies)*
   - Forgot ☐ *1=Yes, 2=no*
   - Allergic to ITN ☐ 1=*Yes, 2=no*
   - Did not sleep at home ☐ *1=Yes, 2=no*
   - Was used by others ☐ *1=Yes, 2=no*
   - Other specify _____
5. Do you use any of the following malaria control measures (tick **ALL** that apply)
   - Indoor Residual Spraying (IRS) ☐ *1=Yes, 2=No*
   - Coils ☐ *1=Yes, 2=No*
   - Body repellents ☐ *1=Yes, 2=No*
   - Sprays e.g. Doom ☐ *1=Yes, 2=No*
   - Traditional medication ☐ *1=Yes, 2=No*
   - None ☐ *1=Yes, 2=No*
   - Others specify _____
6. When you suspect that your child has malaria, what action do you take*? (Tick **ALL** that apply)*

Go to the hospital ☐ *1=Yes, 2=No,* Buy medication from pharmacy/shops ☐ *1=Yes,2=No,* Do tepid sponging ☐ *1=Yes, 2=No*, Traditional medication ☐ *1=Yes, 2=No*,

CHILD'S MEDICAL & NUTRITIONAL HISTORY

7. Is the child still breastfeeding? ☐ *1=Yes, 2=No*

If no, when did child stop breastfeeding ☐☐/ ☐☐/☐☐ (*dd/mm/yy)*

Estimate duration of breast-feeding, or time since stopped? in weeks ☐☐

(Not relevant if have date stopped)

Specify reasons for stopping breastfeeding *(tick **ALL** that apply)*

Child stopped ☐ *1Yes, 2=No,* Child has mouth sores ☐*1=Yes, 2=No,* Started formula ☐*1=Yes, 2=No*, Mother busy ☐*1=Yes, 2=No*, Fear of stigma & discrimination ☐*1=Yes, 2=No,* Stopped cotrimoxazole ☐ *1=Yes, 2=No*, Mother sick ☐ *1=Yes, 2=No* Mother died ☐ *1=Yes, 2=No*

Specify other reasons for stopping breast-feeding _____

8. Is child taking added feeds ☐ *1=Yes, 2=No*

If yes name type of feeds:

Plain Porridge ☐ *1=yes, 2=No,* Fortified Porridge ☐ *1=yes, 2=No,* ☐ Formula milk ☐ *1=yes, 2=No,* ☐ Any other Milk ☐ *1=yes, 2=No,* ☐ Normal Diet☐ *1=yes, 2=No*, Other Specify _____

9. Is child taking cotrimoxazole prophylaxis ☐ *1=Yes, 2=No* **(*if yes GO TO Q10 – IF no continue)***

If no, specify reason **(***tick **ALL** that apply***)**

Child refuses ☐*1=Yes, 2=No,* forgot ☐*1=Yes, 2=No,* ☐ Side effects☐ *1=Yes, 2=No*, fear of stigma & discrimination☐ *1=Yes, 2=No*, Cot out of stock☐ *1=Yes, 2=No*, tired of giving child medication☐ *1=Yes, 2=No*, Child stopped breastfeeding,

Specify other reasons for not taking cotrimoxazole _____

10. Have you visited another health facility since last study contact? ☐ *1=Yes, 2=No*

If yes, indicate date ☐☐/☐☐/☐☐ specify the diagnosis_____

11. Was child admitted during this time? ☐ *1=Yes, 2=No*

12. Were any laboratory tests done on your child? ☐ *1=Yes, 2=No*

If yes, specify MPs☐ *1=Yes, 2=No* Hb ☐ 1*=Yes, 2=No* Full Blood Count ☐ *1=Yes, 2=No*

Urine ☐ *1=Yes, 2=No*

Malaria results ☐*1=Positive, 2= Negative*

Other laboratory test done _____

13. What treatment did your child receive?

Anti-malarials given**?** ☐ *1=Yes, 2=No,* ☐ *1=Yes, 2=No **if yes which one?***

Artemether Lumafantrine (AL) ☐ *1=Yes, 2=No* Sulphadoxine Pyrimethamine (SP) ☐*1=Yes, 2=No* Quinine Sulphate ☐ *1=Yes, 2=No* Amodiaquine Artesunate ☐*1=Yes, 2=No*

14. Antibiotics given? ☐*1=Yes, 2=No, **if yes tick that apply***

Amoxycillin ☐*1=Yes, 2=No* Chloramphenicol ☐ *1=Yes, 2=No*

Erythromycin ☐ *1=Yes, 2=No* Augmentin ☐*1=Yes, 2=No*

Ceftriaxone ☐ *1=Yes, 2=No* Benzyl Penicillin ☐ 1=*Yes, 2=No*
Gentamycin ☐ *1=Yes, 2=No*
Other drugs given? ☐ *1=Yes, 2=No* ***if yes specify drug details***

Drug details of other drugs given

Drug	Dose (mgs/tablets) & frequency	Duration (days)

15. Is child currently sick? ☐ *1=Yes, 2=No*
If yes, advise to take the child to study clinic
16. Anthropometric measurements
Weight ☐☐.☐ *Kg* **length** ☐☐.☐ *Cm* **MUAC** ☐☐ *cm*

SECTION B: NON-HIV EXPOSED

MOTHER'S HEALTH STATUS

1. Is the mother alive? ☐ *1=Yes, 2=No* If yes **GO TO QUESTION 16**
If No, Did death occur since last visit? ☐ *1=Yes, 2=No*
If yes, indicate date**:** ☐☐ / ☐☐/☐☐ and **SKIP TO QUESTION 17**
2. Is the mother on any long-term treatment? ☐ ***1=Yes, 2=No*** *if no, SKIP TO QUESTION 3*
If yes (tick ALL that apply)
TB treatment ☐*1=Yes, 2=No,* Antihypertensives ☐ *1=Yes, 2=No,* anti asthmatics ☐*1=Yes, 2=No,* anti-epileptics ☐ *1=Yes, 2=No,* ant fungals ☐*1=Yes, 2=No,* diabetes drugs ☐ *1=Yes, 2=No*. Other Specify _____

MALARIA CONTROL MEASURE

3. How many mosquito nets are in the home since last visit ☐☐ *1=0, 2=≥1*, If answer is 0, **GO TO Q19**

4. Did child sleep under a mosquito net last night? ☐ *1=Yes, 2=no (No, go to Q2b)*
If yes; is net treated with insecticide? ☐ *1=Yes, 2=No, 3=Not known*
If no, specify reason *(tick **ALL** that applies)*
Forgot ☐
Allergic to ITN ☐
Did not sleep at home ☐
Was used by others ☐
Other specify _____
5. Since the last visit have you used any of the following malaria control measures (tick **ALL** that apply)
Indoor Residual Spraying (IRS) ☐ *1=Yes, 2=No*
Coils ☐ *1=Yes, 2=No*
Body repellents ☐ *1=Yes, 2=No*
Sprays e.g. Doom ☐ *1=Yes, 2=No*

Traditional medication ☐ *1=Yes, 2=No*
None ☐ *1=Yes, 2=No*
Others specify _____

6. When you suspect that your child has malaria, what action do you take*? (Tick **ALL** that apply)*

Go to the hospital ☐*1=Yes, 2=No,* Buy medication from pharmacy/shops ☐*1=Yes, 2=No,* Do tepid sponging ☐*1=Yes, 2=No,* Traditional medication ☐*1=Yes, 2=No,*

CHILD'S MEDICAL & NUTRITIONAL HISTORY

7. Is the child still breastfeeding? ☐ *1=Yes, 2=No*

If no, when did child stop breastfeeding ☐☐/ ☐☐/☐☐ (*dd/mm/yy)*

Estimate duration in weeks ☐☐

(Not relevant if have date stopped)

Specify reasons for stopping breastfeeding *(tick **ALL** that apply)*

Child stopped ☐ *1=Yes, 2=No,* Child has mouth sores ☐ *1=Yes, 2=No,* Started formula ☐ *1=Yes, 2=No,* Mother busy ☐*1=Yes, 2=No,* Mother sick ☐*1=Yes, 2=No,* Mother died☐*1=Yes, 2=No*

Specify other reasons for stopping breast-feeding _____

8. Is child taking added feeds ☐ *1=Yes, 2=No*

If yes name types of feeds

Plain Porridge ☐ *1=Yes, 2=No,* Fortified Porridge ☐ *1=Yes, 2=No,* Formula milk ☐ *1=Yes, 2=No,* Any other Milk ☐*1=Yes, 2=No,* Normal Diet ☐ *1=Yes, 2=No*

Other Specify _____

9. Have you visited another health facility since last study contact? ☐ *1=Yes, 2=No*

If yes, indicate date ☐☐/☐☐/☐☐ specify the diagnosis _____

10. Was child admitted during this time? ☐*1=Yes, 2= No*

11. Were any laboratory tests done on your child? ☐ *1=Yes, 2=No*

If yes, specify ☐ 1= MPs, 2= Hb, 3= Full Blood Count, 4= Urine

Malaria test result ☐*1=positive, 2=negative*

Other laboratory test done _____

12. What treatment did your child receive?

Anti-malarials given? ☐ 1=*Yes, 2=No, **if yes tick that apply***

Artemether Lumafantrine (AL) ☐ 1=*Yes, 2=No,* Sulphadoxine Pyrimethamine (SP) ☐ 1=*Yes, 2=No,* Quinine Sulphate ☐ 1=*Yes, 2=No,* Amodiaquine Artesunate ☐1=*Yes, 2=No*

13. Antibiotics given? ☐ *1=Yes, 2=No* if ***yes tick that apply***

Amoxycillin ☐ *1=Yes, 2=No,* Chloramphenicol ☐ *1=Yes, 2=No,* Erythromycin ☐*1=Yes, 2=No,* Augmentin ☐*1=Yes, 2=No,* Ceftriaxone ☐ *1=Yes, 2=No,* Benzyl Penicillin ☐ **1**=*Yes, 2=No,* Gentamycin ☐ 1=*Yes, 2=No*

Other drugs given? ☐ *1=Yes, 2=No **if yes specify drug details***

Drug details of other drugs given

Drug	**Dose (mgs/tablets) & frequency**	**Duration (days)**

14. Is child currently sick? ☐ *1=Yes, 2=No* If **yes, advise to take the child to study clinic**
15. Anthropometric Measurements
Weight☐☐.☐ *Kg* **Length** ☐☐.☐ *Cm* **MUAC** ☐☐ *cm*

SECTION C

OUTCOME: Action taken ☐ 1 = Admission, 2 = Rx + extra FU, 3 = Rx +no FU, 4 = No action, 5= Completed
Outcome ☐ 1= *Continuing, 2= Study End, 3= Withdrawn, 4=Dead,*

Appendix 5: Clinic follow up Case Report Form (visit 6 for HIV exposed children)

Malaria rebound in HIV exposed children after stopping cotrimoxazole prophylaxis

Form Completed by ☐☐☐ *(Initials)*
Date Form Completed ☐☐ / ☐☐ / ☐☐ *(dd/mm/yy)*
Client Initials ☐☐☐ *(Initials)*
Type of Visit ☐ 1=*Visit 2,2= Visit 3,3=Visit 4,4=Visit 5, 5=Visit 7, 6=Visit 8, 7=Visit 9, 8=Visit 10, Visit 11.*
Type of Client ☐ *1=HIV exposed, 2=non-HIV exposed*

If the subject is HIV exposed go to Section A, if non-HIV exposed go to SECTION B

SECTION A: HIV Exposed

MOTHER'S HEALTH STATUS

1. Is the mother alive? ☐ *1=Yes, 2=No* If yes *GO TO QUESTION 2*
If No, Did death occur since last visit? ☐ *1=Yes, 2=No*
If yes, indicate date: ☐☐ / ☐☐/☐☐ and SKIP TO QUESTION 4
2. Is the mother on any long-term treatment? ☐ *1=Yes, 2=No if no, SKIP TO* QUESTION 3 If yes *(tick ALL that apply)*

ART ☐*1=Yes, 2=No*, TB treatment ☐*1=Yes, 2=No*, Cotrimoxazole prophylaxis ☐ *1=yes, 2=No*, Vincristine ☐*1=Yes, 2=No*, Antihypertensives ☐*1=Yes, 2=No*, ant asthmatics ☐*1=Yes, 2=No*, ant-epileptics ☐*1=Yes, 2=No*, ant fungals ☐*1=Yes, 2=No* diabetes drugs ☐*1=Yes, 2=No*, Other Specify _____

MALARIA CONTROL MEASURES

3. How many mosquito nets are in the home since last visit ☐☐ *1=0, 2=≥1.* If answer is 0, **GO TO Q5**
4. Did child sleep under a mosquito net last night? ☐ *1=Yes, 2=no (No, go to Q4b)*
If yes; is net treated with insecticide? ☐ *1=Yes, 2=No, 3=Not known*
If no, specify reason *(tick **ALL** that applies)*

Forgot ☐ *1=Yes, 2=no*
Allergic to ITN ☐ 1=*Yes, 2=no*
Did not sleep at home ☐ *1=Yes, 2=no*
Was used by others ☐ *1=Yes, 2=no*
Other specify _____

5. Do you use any of the following malaria control measures (tick **ALL** that apply)

Indoor Residual Spraying (IRS) ☐ *1=Yes, 2=No*
Coils ☐ *1=Yes, 2=No*
Body repellents ☐ *1=Yes, 2=No*
Sprays e.g. Doom ☐ *1=Yes, 2=No*
Traditional medication ☐ *1=Yes, 2=No*
None ☐ *1=Yes, 2=No*

Others specify _____

6. When you suspect that your child has malaria, what action do you take*? (Tick **ALL** that apply)*

Go to the hospital ☐*1=Yes, 2=No,* Buy medication from pharmacy/shops ☐ *1=Yes,2=No,* Do tepid sponging ☐*1=Yes, 2=No,* Traditional medication ☐*1=Yes, 2=No*,

CHILD'S MEDICAL & NUTRITIONAL HISTORY

7. Is the child still breastfeeding? ☐ *1=Yes, 2=No*

If no, when did child stop breastfeeding ☐☐/ ☐☐/☐☐ (*dd/mm/yy)*

Estimate duration of breast-feeding, or time since stopped? in weeks ☐☐

(Not relevant if have date stopped)

Specify reasons for stopping breastfeeding *(tick **ALL** that apply)*

Child stopped ☐ *1Yes, 2=No,* Child has mouth sores ☐*1=Yes, 2=No,* Started formula ☐*1=Yes, 2=No,* Mother busy ☐*1=Yes, 2=No,* Fear of stigma & discrimination ☐*1=Yes, 2=No,* Stopped cotrimoxazole ☐ *1=Yes, 2=No,* Mother sick ☐ *1=Yes, 2=No* Mother died ☐ *1=Yes, 2=No*

Specify other reasons for stopping breast-feeding _____

8. Is child taking added feeds ☐ *1=Yes, 2=No*

If yes name type of feeds:

Plain Porridge ☐ *1=yes, 2=No,* Fortified Porridge ☐ *1=yes, 2=No,* ☐ Formula milk ☐ *1=yes, 2=No,* ☐ Any other Milk ☐ *1=yes, 2=No,* ☐ Normal Diet☐ *1=yes, 2=No,* Other Specify _____

9. Is child taking cotrimoxazole prophylaxis ☐ *1=Yes, 2=No* **(*if yes GO TO Q10 – IF no continue)***

If no, specify reason (*tick **ALL** that apply*)

Child refuses ☐*1=Yes, 2=No,* forgot ☐*1=Yes, 2=No,* ☐ Side effects☐ *1=Yes, 2=No,* fear of stigma & discrimination☐ *1=Yes, 2=No,* Cot out of stock☐ *1=Yes, 2=No*, tired of giving child medication☐ *1=Yes, 2=No,* Child stopped breastfeeding,

Specify other reasons for not taking cotrimoxazole _____

10. Have you visited another health facility since last study contact? ☐ *1=Yes, 2=No*

If yes, indicate date ☐☐/☐☐/☐☐ specify the diagnosis_____

11. Was child admitted during this time? ☐ *1=Yes, 2=No*

12. Were any laboratory tests done on your child? ☐ *1=Yes, 2=No*

If yes, specify MPs☐ *1=Yes, 2=No* Hb ☐ 1*=Yes, 2=No* Full Blood Count ☐ *1=Yes, 2=No*

Urine ☐ *1=Yes, 2=No*

Malaria results ☐*1=Positive, 2= Negative*

Other laboratory test done _____

13. What treatment did your child receive?

Anti-malarials given**?** ☐ *1=Yes, 2=No,* ☐ *1=Yes, 2=No* ***if yes which one?***

Artemether Lumafantrine (AL) ☐ *1=Yes, 2=No* Sulphadoxine Pyrimethamine (SP) ☐*1=Yes, 2=No* Quinine Sulphate ☐ *1=Yes, 2=No* Amodiaquine Artesunate ☐*1=Yes, 2=No*

Antibiotics given? ☐ *1=Yes, 2=No, **if yes tick that apply***

Amoxycillin ☐ *1=Yes, 2=No* Chloramphenicol ☐ *1=Yes, 2=No*

Erythromycin ☐ *1=Yes, 2=No* Augmentin ☐ *1=Yes, 2=No*

Ceftriaxone ☐ *1=Yes, 2=No* Benzyl Penicillin ☐ 1=*Yes, 2=No*

Gentamycin ☐ *1=Yes, 2=No*

Other drugs given? ☐ *1=Yes, 2=No* ***if yes specify drug details***

Drug details of other drugs given

Drug	**Dose (mgs/tablets) & frequency**	**Duration (days)**

14. Anthropometric measurements

Weight ☐☐.☐ *Kg* **length** ☐☐.☐ *Cm* **MUAC** ☐☐ *cm*

15. HIV Testing

Blood Sample for HIV PCR testing collected? ☐ *1=Yes, 2=No*

If No, Specify reasons:_____

_____

HIV Rapid testing result ☐ *1=positive, 2=Negative*

16. Has mother been given Carbergoline? ☐ *1=Yes, 2=No*

If No, Specify reason:_____

Appendix 6: Clinic follow up Case Report Form (visit 7 for HIV exposed children)

Malaria rebound in HIV exposed children after stopping cotrimoxazole prophylaxis

Form Completed by ☐☐☐ *(Initials)*
Date Form Completed ☐☐ / ☐☐ / ☐☐ *(dd/mm/yy)*
Client Initials ☐☐☐ *(Initials)*
Type of Visit ☐ 1=*Visit 2,2= Visit 3,3=Visit 4,4=Visit 5, 5=Visit 7, 6=Visit 8, 7=Visit 9, 8=Visit 10, Visit 11.*
Type of Client ☐ *1=HIV exposed, 2=non-HIV exposed*
If the subject is HIV exposed go to Section A, if non-HIV exposed go to SECTION B

SECTION A: HIV Exposed

MOTHER'S HEALTH STATUS

1. Is the mother alive? ☐ *1=Yes, 2=No* If yes *GO TO QUESTION 2*
If No, Did death occur since last visit? ☐ *1=Yes, 2=No*
If yes, indicate date: ☐☐ / ☐☐/☐☐ and SKIP TO QUESTION 4
2. Is the mother on any long-term treatment? ☐ *1=Yes, 2=No if no, SKIP TO* QUESTION 3 If yes *(tick ALL that apply)*
ART ☐*1=Yes, 2=No,* TB treatment ☐*1=Yes, 2=No,* Cotrimoxazole prophylaxis ☐ *1=yes, 2=No,* Vincristine ☐*1=Yes, 2=No,* Antihypertensives ☐*1=Yes, 2=No,* ant asthmatics ☐*1=Yes, 2=No,* ant-epileptics ☐*1=Yes, 2=No,* ant fungals ☐*1=Yes, 2=No* diabetes drugs ☐*1=Yes, 2=No,* Other Specify _____

MALARIA CONTROL MEASURES

3. How many mosquito nets are in the home since last visit ☐☐ *1=0, 2=≥1.* If answer is 0, **GO TO Q5**
4. Did child sleep under a mosquito net last night? ☐ *1=Yes, 2=no (No, go to Q4b)*
If yes; is net treated with insecticide? ☐ *1=Yes, 2=No, 3=Not known*
If no, specify reason *(tick **ALL** that applies)*
Forgot ☐ *1=Yes, 2=no*
Allergic to ITN ☐ 1=*Yes, 2=no*
Did not sleep at home ☐ *1=Yes, 2=no*
Was used by others ☐ *1=Yes, 2=no*
Other specify _____
5. Do you use any of the following malaria control measures (tick **ALL** that apply)
Indoor Residual Spraying (IRS) ☐ *1=Yes, 2=No*
Coils ☐ *1=Yes, 2=No*
Body repellents ☐ *1=Yes, 2=No*
Sprays e.g. Doom ☐ *1=Yes, 2=No*
Traditional medication ☐ *1=Yes, 2=No*
None ☐ *1=Yes, 2=No*
Others specify _____

6. When you suspect that your child has malaria, what action do you take*? (Tick **ALL** that apply)*

Go to the hospital ☐*1=Yes, 2=No,* Buy medication from pharmacy/shops ☐ *1=Yes,2=No,* Do tepid sponging ☐*1=Yes, 2=No,* Traditional medication ☐*1=Yes, 2=No,*

CHILD'S MEDICAL & NUTRITIONAL HISTORY

7. Is the child still breastfeeding? ☐ *1=Yes, 2=No*

If no, when did child stop breastfeeding ☐☐/ ☐☐/☐☐ (*dd/mm/yy)*

Estimate duration of breast-feeding, or time since stopped? in weeks ☐☐

(Not relevant if have date stopped)

Specify reasons for stopping breastfeeding *(tick **ALL** that apply)*

Child stopped ☐ *1Yes, 2=No,* Child has mouth sores ☐*1=Yes, 2=No,* Started formula

☐*1=Yes, 2=No,* Mother busy ☐*1=Yes, 2=No,* Fear of stigma & discrimination

☐*1=Yes, 2=No,* Stopped cotrimoxazole ☐ *1=Yes, 2=No,* Mother sick ☐ *1=Yes,*

2=No Mother died ☐ *1=Yes, 2=No*

Specify other reasons for stopping breast-feeding _____

8. Is child taking added feeds ☐ *1=Yes, 2=No*

If yes name type of feeds:

Plain Porridge ☐ *1=yes, 2=No,* Fortified Porridge ☐ *1=yes, 2=No,* ☐ Formula milk ☐ *1=yes, 2=No,* ☐ Any other Milk ☐ *1=yes, 2=No,* ☐ Normal Diet☐ *1=yes, 2=No,* Other Specify _____

9. Is child taking cotrimoxazole prophylaxis ☐ *1=Yes, 2=No* **(*if yes GO TO Q10 – IF no continue)***

If no, specify reason (*tick **ALL** that apply*)

Child refuses ☐*1=Yes, 2=No,* forgot ☐*1=Yes, 2=No,* ☐ Side effects☐ *1=Yes, 2=No,* fear of stigma & discrimination☐ *1=Yes, 2=No,* Cot out of stock☐ *1=Yes, 2=No,* tired of giving child medication☐ *1=Yes, 2=No,* Child stopped breastfeeding,

Specify other reasons for not taking cotrimoxazole _____

10. Have you visited another health facility since last study contact? ☐ *1=Yes, 2=No*

If yes, indicate date ☐☐/☐☐/☐☐ specify the diagnosis_____

11. Was child admitted during this time? ☐ *1=Yes, 2=No*

12. Were any laboratory tests done on your child? ☐ *1=Yes, 2=No*

If yes, specify MPs☐ *1=Yes, 2=No* Hb ☐ 1=*Yes, 2=No* Full Blood Count ☐ *1=Yes, 2=No*

Urine ☐ *1=Yes, 2=No*

Malaria results ☐*1=Positive, 2= Negative*

Other laboratory test done _____

13. What treatment did your child receive?

Anti-malarials given**?** ☐ *1=Yes, 2=No,* ☐ *1=Yes, 2=No* ***if yes which one?***

Artemether Lumafantrine (AL) ☐ *1=Yes, 2=No* Sulphadoxine Pyrimethamine

(SP) ☐ *1=Yes, 2=No* Quinine Sulphate ☐ *1=Yes, 2=No* Amodiaquine
Artesunate ☐ *1=Yes, 2=No*

Antibiotics given? ☐ *1=Yes, 2=No*, ***if yes tick that apply***

Amoxycillin ☐ *1=Yes, 2=No* Chloramphenicol ☐ *1=Yes, 2=No*
Erythromycin ☐ *1=Yes, 2=No* Augmentin ☐ *1=Yes, 2=No*
Ceftriaxone ☐ *1=Yes, 2=No* Benzyl Penicillin ☐ 1=*Yes, 2=No*
Gentamycin ☐ *1=Yes, 2=No*

Other drugs given? ☐ *1=Yes, 2=No* ***if yes specify drug details***

Drug details of other drugs given

Drug	**Dose (mgs/tablets) & frequency**	**Duration (days)**

14. Anthropometric measurements

Weight ☐☐.☐ *Kg* **length** ☐☐.☐ *Cm* **MUAC** ☐☐ *cm*

15. HIV PCR RESULTS

HIV PCR Results ☐ *1- Positive, 2=Negative*

If Negative, has child stopped cotrimoxazole ☐ *1=Yes, 2=No*

If Positive, has child been referred to ART Clinic ☐ *1=Yes, 2=No*

Appendix 7: Sick Visit Case Report Form
Malaria rebound in HIV exposed children after stopping cotrimoxazole prophylaxis

Form Completed by ☐☐☐ *(Initials*
Patient Initials ☐☐☐ *(Initials)*
Date of Visit ☐☐ / ☐☐ / ☐☐ *(dd/mm/yy)*
Type of Case ☐ *1=HIV exposed, 2=non-HIV exposed*

CHILD'S MEDICAL & NUTRITIONAL HISTORY

1. Is the child still breastfeeding? ☐ 1=*Yes, only breastfed*, 2=*Yes & added feeds, 2=No*

If no, specify reason *(tick **ALL** that apply)*

Child stopped ☐ *1=Yes, 2=No,* Child has mouth sore ☐ *1=Yes 2=No,* Started formula ☐ *1=Yes 2=No* Mother busy ☐ *1=Yes 2=No,* Fear of stigma & discrimination ☐ *1=Yes 2=No* Mother sick ☐ *1=Yes 2=No,* Mother died ☐ *1=Yes 2=No;* Other specify Other specify _____

2. Is child taking cotrimoxazole prophylaxis **(FOR HIV Exposed ONLY)** ☐ *1=Yes, 2=No* ***(IF YES GO TO Q3, IF no continue)***

If no, specify reason (*tick **ALL** that apply*)

Child refuses ☐ *1=Yes 2=No* forgot ☐ 1= Yes, *2=No* Side effects ☐*1=Yes 2= No* fear of stigma & discrimination ☐ *2=No 1=Yes* CPT out of stock ☐ *1=Yes 2=No,* tired of giving child medications☐ *1=Yes, 2=No,* Child stopped breastfeeding ☐ *1=Yes 2=No,* Specify other reasons for not taking cotrimoxazole

_____

3. Have you visited another health facility since last study contact? ☐ *1=Yes, 2=No* ***(if no go to CURRENT MEDICAL HISTORY)***

If yes, specify type of facility

Health Centre ☐ *1=Yes, 2=No*
Private Clinic ☐ *1=Yes, 2=No*
Traditional healer ☐ *1=Yes, 2=No*
Other specify _____

(Check health passport for details and complete the following)

Indicate date ☐☐/☐☐/☐☐ specify diagnosis _____

4. Was child admitted during this time? ☐ *1=Yes, 2=No*
5. Were any laboratory tests done on your child? ☐ *1=Yes, 2=No*

If yes, specify ☐*1= MPs, 2= Hb, 3=Full Blood Count, 4= Urine*
Other laboratory test done _____
Malaria test results ☐ 1=*Positive, 2=Negative*

6. Did child receive any treatment ☐ *1=Yes, 2=No*

if No go to Section B: Current Medical History

Anti-malarials given? ☐ 1=*Yes*, 2=*No* ***if yes tick that apply***

☐ *1=*Artemether Lumafantrine *(AL)* ***2=***Sulphadoxine Pyrimethamine (SP), *3=* Quinine Sulphate *4=* Amodiaquine Artesunate

Antibiotics given? ☐ 1=*Yes, 2= No **if yes tick that apply***

Amoxycillin ☐*1=Yes*, 2=*No* *Chloramphenicol* ☐ *1=Yes 2=No*

Erythromycin ☐ *1=Yes, 2=No* *Augmentin* ☐ *1=Yes 2=No*
Ceftriaxone ☐*1=Yes, 2=No* *Benzyl Penicillin* ☐*1=Yes 2=No*
Gentamycin ☐ *1=Yes, 2=No*

Other drugs given? ☐ 1=*Yes, 2=No* ***if yes specify drug details***

Drug details of other drugs given

Drug	**Dose (mgs/tablets) & frequency**	**Duration (days)**

CURRENT MEDICAL HISTORY

7. Presenting problems **a)** ☐☐☐ *Code and Specify* ____
b) ☐☐☐ *Code and Specify* _____

Symptoms

Fever ☐*1=Yes 2=No* for how long? ☐☐ *days*
Cough ☐*1=Yes 2=No* for how long? ☐☐ *days*
Vomiting ☐ *1=Yes 2=No* for how long? ☐☐ *days*
Diarrhea ☐ *1=Yes 2=No* for how long? ☐☐ *days*
Fitting ☐ *1=Yes 2=No* for how long? ☐☐ *days*
Respiratory distress ☐ *1=Yes 2=No* for how long? ☐☐ *days*
Rash ☐ *1=Yes 2=No* for how long? ☐☐ *days*
Other (*please specify*) _____ for how long? ☐☐ *days*

CLINICALEXAMINATION

8. Anthropometric measurements

Weight ☐☐.☐ *Kg;* **Height** ☐☐.☐ *cm* **MUAC** ☐☐.☐ cm

9. VITAL SIGNS

Temperature ☐☐.☐ °C Respiratory rate ☐☐☐ */min* Pulse Rate ☐☐☐ b/min

10. OTHER SIGNS

Loss of consciousness ☐ *1=Yes, 2=No* Lymph nodes ☐ *1=Yes, 2=No*

Convulsions ☐ *1=Yes, 2=No* Jaundice ☐ *1=Yes, 2=No*
Mouth ulcers ☐ *1=Yes, 2=No* Skin Rash ☐ *1=Yes, 2=No*
Chest signs ☐ *1=Yes, 2=No* Fungal infection ☐ *1=Yes, 2=No*
Dehydration ☐ *1=Yes, 2=No*
Pallor ☐ *1=Yes, 2=No*
Spleen ☐☐ *cm*
Liver ☐☐ *cm*

LAB INVESTIGATIONS : Please complete Appropriate laboratory form

Hb ☐☐.☐ g/dl
Malaria RDT ☐ *1=positive, 2= negative*

Malaria slide ☐ *1=positive, 2=negative*
If positive, Severity ☐ *1=1+, 2=2+, 3=3+, 4=4+*
Filter paper ☐ *1= Collected, 2= Not Collected*

DIAGNOSES

Presenting diagnosis 1 ☐☐☐☐ *Code and Specify*_____
Presenting diagnosis 2 ☐☐☐☐*Code and Specify* _____

TREATMENT

Anti-malarials given? ☐ *1=Yes, 2=No*
Antibiotics given? ☐ *1=Yes, 2=No*
Other drug given? ☐ *1=Yes, 2=No*

Drug details of anti-malarials, antibiotics and other drugs given

Drug	***Dose (mgs/tablets) & frequency***	***Duration (days)***

VISIT OUTCOME

Action taken ☐ 1 = *Admission, 2 = Rx + extra FU, 3 = Rx +no FU, 4 = No action, 5= Completed*
Outcome ☐ 1= *Continuing, 2= Study End, 3= Withdrawn, 4=Dead, 5= Discontinue study drugs*

Appendix 8: Laboratory Form

Malaria rebound in HIV exposed children after stopping cotrimoxazole prophylaxis

Form completed by ☐☐☐ *(Initials)*
Date ☐☐ / ☐☐ / ☐☐
Client's Initials ☐☐
Type of client ☐ *1=HIV exposed, 2= non-HIV exposed*
Visit ☐*visit 1=1 sick visit=2, visit 12=3*

Samples

Thick film☐*1=Yes, 2=No, (if no, specify reason ____)*
Thin film☐*1=Yes, 2=No (if no specify reason _____)* Filter paper☐***1=Yes, 2=No, (If no, specify reason _____)***

Form completed by ☐☐☐ **(in the Laboratory)**

Samples received in Laboratory

Thick Film ☐ *1=Yes, 2=No (if no, specify reason_____)*
Thin film ☐*1=Yes, 2=No (if no, specify reason_____)*
Filter Paper ☐*1=Yes, 2=No, (If no, specify reason_____)*
Blood film result
Malaria Parasite Density
First reader ☐☐☐☐☐ *parasites/200wbc* **Initials** ☐☐☐
Second reader ☐☐☐☐☐ ***parasites/200wbc*** Initials ☐☐☐
Malaria microscopy ☐ *1=positive, 2=negative*
Malaria Rapid Test ☐ *1=positive, 2=negative*
Malaria species: ☐ **1=*P. falciparum*, 2= *P. malariae*, 3= *P. ovale*, 4=*P. vivax***
Filter Paper done ☐ 1=*Yes, 2=No*

IF APPLICABLE,
Full Blood Count:

WBC (total) ☐☐☐.☐ $10^3/\mu L$		**MCV**	☐☐☐.☐ *fL*
RBC ☐☐.☐	$10^6/\mu L$	**MCHC**	☐☐.☐ *g/dL*
Hb ☐☐.☐	*g/dL*	**RDW**	☐☐.☐ *%*
Hct ☐☐.☐	*%*	**Plt**	☐☐☐ $10^3/\mu L$
		MCH	☐☐.☐ *g/dL*

Appendix 9: Last study visit Case Report Form (visit 12)

Malaria rebound in HIV exposed children after stopping cotrimoxazole prophylaxis

Form Completed by ☐☐☐ *(Initials)*
Date Form Completed ☐☐ / ☐☐ / ☐☐ *(dd/mm/yy)*
Client Initials ☐☐☐ *(Initials)*
Type of Client ☐ *1=HIV exposed, 2=non-HIV exposed*

MOTHER'S HEALTH STATUS

1. Is the mother alive? ☐ *1=Yes, 2=No* If yes *GO TO QUESTION 2*
   If No, Did death occur since last visit? ☐ *1=Yes, 2=No*
   If yes, indicate date: ☐☐ / ☐☐/☐☐ and SKIP TO QUESTION 3
2. Is the mother on any long-term treatment? ☐ *1=Yes, 2=No if no, SKIP TO QUESTION 3*

If yes (tick ALL that apply)

ART ☐*1=Yes, 2=No, TB treatment* ☐ *1=Yes, 2=No, Cotrimoxazole prophylaxis* ☐ *1=Yes, 2=No,* Vincristine ☐*1=Yes, 2=No,* Antihypertensives ☐*1=Yes, 2=No, ant* asthmatics ☐*1=Yes, 2=No,* ant-epileptics ☐*1=Yes, 2=No,* ant fungals ☐*1=Yes, 2=No,* diabetes drugs ☐*1=Yes, 2=No,* Other Specify

_____

(For questions 3 & 4, check in health passport or mothers HIV care records for HIV exposed only)

3. Was CD4 Count of mother measured since last visit? ☐ *1=Yes, 2=no (if no,* ***GO TO Q4)***

If yes, record ☐☐☐ */mm*^{3} *Date* ☐☐/☐☐/☐☐ *(dd/mm/yy)*

4. Was Viral Load of Mother measured since the last visit? ☐ *1= Yes, 2=No* (if No, **GO TO Q5**) If Yes, Is it detectable? ☐ *1= Detectable, 2=Not Detectable*

If detectable, record ☐☐☐☐☐☐☐ *copies/ml Date* ☐☐/☐☐/☐☐ (*dd/mm/yy)*

MALARIA CONTROL MEASURES

5. How many mosquito nets are in use in the home since last visit? ☐☐ *1=0, 2=≥1,* If answer is 1, **GO TO Q10**
6. Did child sleep under a mosquito net last night? ☐ *1=Yes, 2=no* ***(No, go to Q9)***

If yes, is net treated with insecticide? ☐ *1=Yes, 2=No, 3=Not known*

7. When was the last time net was treated since enrolment into the study? ☐

*1=never, 2=past three, 3=past six months, 4=past 9 months, 5= past year, 5=Other Specify*_____

8. How often do you treat mosquito nets ☐ *1= never, 2=0nce a year, 3=once in 6 months, 4=not known*

If no, specify reason *(tick **ALL** that applies)*

Forgot ☐ *1=Yes, 2=No*
Allergic to ITN ☐*1=Yes, 2=No*
Did not sleep at home ☐*1=Yes, 2=No*
Was used by others ☐ *1=Yes, 2=No*
Other specify_____

9. Since the last visit have you used any of the following malaria control measures (tick **ALL** that apply)

Indoor Residual Spraying (IRS) ☐ *1=Yes,2=No*
Coils ☐ *1=Yes, 2=No*
Body repellents ☐*1=Yes, 2=No*
Sprays e.g. Doom ☐ *1=Yes, 2=No*
Traditional medication ☐*1=Yes, 2=No*
None ☐ 1=Yes, 2=No

10. When you suspect that your child has malaria, what action do you take*? (Tick **ALL** that apply)*

Go to the hospital ☐*1=Yes, 2=No*
Buy medication from pharmacy/shops ☐*1=Yes, 2=No*
Do tepid sponging ☐*1=Yes, 2=No*
Traditional medication ☐*1=Yes, 2=No*

CHILD'S MEDICAL & NUTRITIONAL HISTORY

11. Is the child still breastfeeding? ☐ *1=Yes, 2=No*

If no, when did child stop breastfeeding ☐☐/ ☐☐/☐☐ (*dd/mm/yy)*
Estimate duration in weeks ☐☐ *(Not relevant if has date stopped)*

Specify reasons for stopping breastfeeding *(tick **ALL** that apply)*

Child stopped, ☐*1=Yes, 2=No* Child has mouth sores ☐*1=Yes, 2=No*
Started formula ☐ *1=Yes, 2=No* Mother busy ☐*1=Yes, 2=No*
Fear of stigma & discrimination ☐*1=Yes, 2=No* Stopped cotrimoxazole ☐ *1=Yes, 2=No*, Mother sick ☐*1=Yes, 2=No* Mother died ☐ *1=Yes, 2=No*
Specify other reasons for stopping breast feeding_____

12. Is child taking added feeds ☐ *1=Yes, 2=No*

If yes name type of Feeds

Plain porridge ☐*1=Yes, 2=No,* Fortified Porridge ☐*1=Yes, 2=No*
Formula milk ☐*1=Yes, 2=No*, Any other Milk ☐*1=Yes, 2=No*
Normal diet ☐*1=Yes, 2=No*,
Other Specify _____

(If non-HIV exposed GO TO Q15)

13. Is child taking cotrimoxazole prophylaxis ☐ *1=Yes, 2=No* **(*if yes GO TO Q15 IF no continue)***

If no, specify reason (*tick **ALL** that apply*)

Child refuses ☐ *1=Yes, 2=No,* forgot ☐ *1=Yes, 2=No* Side effects ☐ *1=Yes, 2=No* fear of stigma & discrimination ☐ *1=Yes, 2=No* CPT out of stock ☐ *1=Yes, 2=No*Child HIV PCR negative ☐ *1=Yes, 2=No,* tired of giving child medications ☐ *1=Yes, 2=No* Child stopped breastfeeding ☐ *1=Yes, 2=No* Specify other reasons for not taking contrimoxazole _____

14. Have you visited another health facility since last study contact? ☐ *1=Yes, 2=No*

If yes, indicate date ☐☐/☐☐/☐☐ specify the diagnosis _____Code☐☐☐☐ Was child admitted during this time*?* ☐*1=Yes, 2=No*

15. Were any laboratory tests done on your child? ☐ *1=Yes, 2=No*

If yes, specify ☐ *1=MPs 2=Hb 3= Full Blood Count 4= Urine*

Other laboratory test done _____

16. What treatment did your child receive?

Anti-malarials given? ☐1= *Yes*, 2= *No* ***if yes tick that apply***

☐ 1=Artemether Lumafantrine (AL), 2=Sulphadoxine Pyrimethamine (SP), 3=Quinine Sulphate, 4=Amodiaquine Artesunate

Antibiotics given? ☐ *1=Yes, 2=No if yes tick that apply*

Amoxycillin ☐*1=Yes, 2=No* Chloramphenicol ☐ *1=Yes, 2=No*, Erythromycin ☐ *1=Yes, 2=No*, Augmentin ☐*1=Yes, 2=No* Ceftriaxone ☐*1=Yes, 2=No*, Benzyl Penicillin ☐ *1=Yes, 2=No* Gentamycin ☐ *1=Yes, 2=No,*

Other drugs given? ☐ *1=Yes, 2=No* ***if yes specify drug details***

Drug details of other drugs given

Drug	**Dose (mgs/tablets) & frequency**	**Duration (days)**

CURRENT MEDICAL STATUS

Is your child having any complaints? ☐ 1=Y*es, 2= No*, IF **NO**, **SKIP TO CLINICAL EXAM**

Fever ☐ *1=Yes, 2=No, If 'yes', duration* ☐☐ days

Cough ☐ 1=*Yes2=No, If 'yes', duration* ☐☐ days

Vomit ☐ 1=*Yes, 2=No, If 'yes', duration* ☐☐ days

Diarrhoea ☐ 1=*Yes*, 2= *No*, If *'yes', duration* ☐☐ days

Rash ☐1= *Yes*, 2=*No, If 'yes', duration* ☐☐ *days*

*Other specify*_____

CLINICAL EXAMINATION

17. Anthropometric Measurements

Weight☐☐.☐ *Kg* **Height** ☐☐.☐ *cm* **MUAC** ☐☐ *cm*

18. Vital signs

Pulse rate ☐☐☐ beats/*min*

Temperature ☐☐.☐ *ºC*

Respiratory rate ☐☐☐ */min*

19. Other Signs

a) Chest signs ☐ 1=*Yes, 2=No* (***If no, go to b)***

If yes, specify (tick **ALL** that apply)

Chest recessions ☐ *1=yes, 2=No*

Crepitations ☐ *1=Yes, 2=No*

Tachypnea ☐ *1=yes, 2=No*

Hyperinflation ☐ *1=Yes, 2=No*

Wheezing ☐*1=Yes, 2=No*

b) Oedema ☐ 1=*Yes, 2=No*.

c) Lymphadenopathy ☐1=*yes, 2=no, If no, go to (d)*

If yes, ☐ 1=*Regional, 2=General*

d) Pallor: Conjunctival ☐ 1=*present*, 2= *absent*, ***if no, go to (e)***

If Conjunctival *present:* ☐ 1=*Mild/moderate,2=Severe*

e) Dehydration ☐1=*yes, 2= no, if no, go to (f)*

If yes ☐ 1=*Mild, 2=Moderate, 3= Severe,*
f) Spleen ☐☐ *cm*
g) Liver ☐☐ *cm*
h) ENT/mouth abnormal ☐ 1=*Yes, 2=No*. ***If yes, specify****:* Thrush☐*1=Yes, 2=No*
Sores ☐*1=Yes, 2=No*
If other, please specify _____
i) Jaundice? ☐ 1=*Yes, 2=No*

20. Lab Investigations: ***Please complete laboratory form***
Hb ☐☐.☐ g/dl
Malaria RDT ☐ 1=*positive, 2=negative*
Malaria slide ☐ *positive*, 2= *negative*
If positive, severity ☐ *1=1+, 2=2+, 3=3+, 4=4+*
Filter paper malaria ☐ *1=Yes, 2=No*
(If non-HIV exposed go, to Diagnosis)
HIV Rapid Test ☐ 1= *positive, 2=negative*

21. Diagnosis
a) *Presenting* diagnosis 1_____☐☐☐☐ *code and Specify* _____
b) Presenting diagnosis 2_____ ☐☐☐☐ *code and Specify* _____

22. Treatment
Anti-malarials given? ☐ *1=Yes, 2=No*
Antibiotics given? ☐ *1=Yes, 2=No*
Other drugs given? ☐ *1=Yes, 2=No*
Drug details of anti-malarials, antibiotics and other drugs given

Drug	**Dose (mgs/tablets) & frequency**	**Duration (days)**

VISIT OUTCOME
Action taken ☐ *1 = Admission, 2 = Rx + extra FU, 3 = Rx +no FU, 4 = No action, 5= Completed Study*
Outcome ☐ *1= Continuing, 2= Study End, 3= Withdrawn, 4=Dead, 5= Discontinue study drugs (if 2: complete summary form, if 3: complete withdrawal form, if 4:fill in verbal autopsy form)*

Appendix10: COMREC Approval letter

UNIVERSITY OF MALAWI

Principal

K.M Maleta, MBBS PhD

Our Ref.:

Your Ref.: P.05/10/954

College of Medicine
Private Bag 360
Chichiri
Blantyre 3
Malawi
Telephone: 877 245
877 291
Fax: 874 700
Telex: 43744

9th March 2011

Dr Kamija Phiri
Postgraduate Dean
College of Medicine
P/Bag 360
Blantyre 3

Dear Dr Phiri,

RE: P.05/10/954 – Malaria rebound in cotrimoxazole prophylactic HIV exposed children

I write to inform you that COMREC reviewed your proposal mentioned above which you resubmitted for expedited review. The following points have been dealt with:

- Copies of the original protocol and consent forms with changes highlighted or tracked have been provided
- Version numbers and dates on the protocol or consent form have now been inserted.

I am pleased to inform you that your protocol **was approved** after considering that you addressed all the queries raised in the initial review.

As you proceed with the implementation of your study we would like you to take note that all requirements by the college are followed as indicated on the attached page.

Sincerely,

Approved by
College of Medicine
- 9 MAR 2011
(COMREC)
Research and Ethics Committee

Prof. J. M. Mfutso Bengo
CHAIRMAN - COMREC

Appendix 11: LSTM Ethics approval

LSTM
LIVERPOOL SCHOOL OF TROPICAL MEDICINE

Pembroke Place,
Liverpool, L3 5QA, UK
Tel: +44 (0)151 705 3100
Fax: +44 (0)151 705 3370
www.liv.ac.uk/lstm

Nyanyiwe Mbeye
Liverpool School of Tropical Medicine
Pembroke Place
Liverpool
L3 5QA

Thursday, 12 May 2011

Dear Nyanyiwe Mbeye

Re: Research Protocol (11.30) Malaria rebound in Cotrimoxazole Prophylactic HIV exposed children (MaRCH)

Thank you for your letter dated 3 May 2011 responding to the points raised by the Research Ethics Committee. The protocol now has formal ethical approval from the Chair of LSTM Research Ethics Committee.

The approval is for a fixed period of three years, renewable annually thereafter. The committee may suspend or withdraw ethical approval at any time if appropriate.

Approval is conditional upon:

- Submission of ethical approval from other ethics committees.
- Notification of all amendments to the protocol for approval before implementation.
- Notification of when the project actually starts.
- Provision of an annual update to the Committee. Failure to do so could result in suspension of the study without further notice.
- Reporting of all severe unexpected Adverse Events to the Committee
- Reporting of new information relevant to patient safety to the Committee
- Provision of Data Monitoring Committee reports (if applicable) to the Committee

Failure to comply with these requirements will result in withdrawal of approval. The Committee would also like to receive copies of the final report once the study is completed.

Yours sincerely

Dr Angela Obasi
Co - Chair, Research Ethics Committee

cc: Feiko ter Kuile, Kamija Phiri

Appendix 12: Informed Consent Form for HIV exposed

Malaria rebound in Cotrimoxazole prophylactic HIV exposed children

Participant Information
This study is being conducted by the College of Medicine of the University of Malawi in collaboration with the University of Liverpool. We invite you and your child to take part in this study. Before you decide it is important for you to understand why the research is being done and what it will involve.

What is the purpose of this study?
The aim of this study is to learn more about malaria, other diseases and practices associated with the use of cotrimoxazole which is used for prevention of HIV related illnesses in children whose mothers are HIV infected. We want to find out whether after stopping cotrimoxazole a child born from an HIV infected mother who remains HIV negative will be at higher risk than normal children of suffering from malaria. This is because it is believed that cotrimoxazole which also treats malaria may be protecting your child from getting malaria. We know that a little malaria for young children is good for the child to build up its immunity. We do not know whether cotrimoxazole which also treats malaria is hindering the development of this immunity. We therefore want to compare children who are born to HIV infected mothers and have been on cotrimoxazole for prevention of HIV related illnesses against those that are born to HIV negative mothers and not been on cotrimoxazole for prevention of HIV related illnesses. A few mothers/guardians will also be asked of their experiences of giving their child cotrimoxazole which prevents HIV related illnesses over the course of the study.

Why has your child been chosen?
Your child has been chosen because he/she is born from an HIV infected mother, is breastfeeding and on daily cotrimoxazole for prevention of HIV related illnesses. Your child will be among 1000 children who will be participating in this study if you choose that your child participate in this study.

What will happen to your child if he/she takes part in the study?
Since your child is too young to answer questions, we will instead ask you a few questions on the health of your child, and malaria control interventions that you practice at home. We will collect about 1 ml of blood from a heel/finger prick (approximately half a teaspoon) from your child for malaria tests and checking of haemoglobin levels whenever your child is sick. This is part of the standard clinical practice when treating a sick child. However, the same blood tests will be done at recruitment, visit 6 (month 12) and visit 12 (month 24). In addition, if your child is one of the children selected to take part in the immunology sub study, about 5 mls (approximately a tablespoonful) of blood will be collected at months 6, 12, 18 & 24 to investigate how your child is building up malaria specific immunity. For these, your child will be asked to come to the study clinic even if he/she is not sick. The scheduled tests including the immunology tests are not part of standard clinical guidelines, but are done specifically for the purpose of this study. All study visits will take place at home with a visit

taking approximately 30 minutes. You will be asked to come back to the clinic with your child when he/she is sick. As a guardian you may be selected to take part in some interviews and group discussions on your lived experiences with administering daily cotrimoxazole for the prevention of HIV related illnesses to a child born to an HIV infected mother.

What are the possible risks for participating in this study?
The study staff will take every effort to protect your information and that of your child. However, the possible risk to your child would be experiencing of some pain when blood is being collected.

What are the benefits for participating in this study?
Apart from study procedures, the study participants will have access to some medical services at the study clinic throughout their participation in the study. A dedicated Clinical Officer will attend to study participants at any point they present to the clinic sick. The participants taking cotrimoxazole will also be monitored for any side effects related to cotrimoxazole and managed according to Ministry of Health and hospital guidelines.

Does your child need to participate in the study?
Participation in the study is entirely voluntary. Even if you agree to participate, you may withdraw your child at any point in time. This will not affect the care that the child will receive at this hospital.

What will participating in the study cost me?
You will not pay anything for participating in this study and we will not pay you for taking part in the study. If you are asked by study staff to come to the study clinic, we will reimburse for the transport costs accordingly.

Who should I contact if I have a problem?
This study will be reviewed and approved by the College of Medicine Research and Ethics Committee (COMREC) and the Liverpool School of Tropical Medicine Ethics Committee. If you have any questions about your rights or the rights of your child for participating in this study, please, contact the chairman of the COMREC Prof. Mfutso-Bengo on telephone number 01871911. You may also contact the study Clinician Mr Zinenani Truwah on 0999413775.

Participant Agreement
I have understood the information contained in this consent form and I hereby voluntarily agree that my child participate in this study.

Name of child participating in the study		Date

Name of the person giving Consent (guardian)	Signature	Date

Name of person obtaining consent	Signature	Date

For illiterate guardians

Thumb Print of guardian

Name of Witness	Signature	Date

Appendix 13: Informed Consent Form for non-HIV exposed children

Malaria rebound in Cotrimoxazole prophylactic HIV exposed children

Participant Information
This study is being conducted by the College of Medicine of the University of Malawi in collaboration with the University of Liverpool. We invite you and your child to take part in this study. Before you decide it is important for you to understand why the research is being done and what it will involve.

What is the purpose of this study?
The aim of this study is to learn more about malaria, other diseases and practices associated with the use of cotrimoxazole which is used for prevention of HIV related illnesses in children whose mothers are HIV infected. We want to find out whether after stopping cotrimoxazole a child born from an HIV infected mother who remains HIV negative will be at higher risk than normal children of suffering from malaria. This is because it is believed that cotrimoxazole which also treats malaria may be protecting your child from getting malaria. We know that a little malaria for young children is good for the child to build up its immunity. We do not know whether cotrimoxazole which also treats malaria is hindering the development of this immunity. We therefore want to compare children who are born to HIV infected mothers and have been on cotrimoxazole for prevention of HIV related illnesses against those that are born to HIV negative mothers and not been on cotrimoxazole for prevention of HIV related illnesses. A few mothers/guardians will also be asked of their experiences of giving their child cotrimoxazole which prevents HIV related illnesses over the course of the study.

Why has your child been chosen?
Your child has been chosen because he/she is born from an HIV negative mother and is breastfeeding. We would like to investigate how your child responds to malaria infection compared to other children who are HIV negative but born from HIV infected mothers. Your child will be among 1000 children who will be participating in this study.

What will happen to your child if he/she takes part in the study? Since your child is too young to answer questions, we will instead ask you a few questions on the health of your child, and malaria control interventions that you practice at home. We will collect some blood specimen (approximately half a teaspoon) from your child for malaria tests and checking for hemoglobin levels whenever your child is sick. This is part of standard clinical practice when treating a sick child. However, the same blood tests will be done at recruitment, at 12 and 24 months. In addition, if your child is one of the children selected to take part in the immunology sub study, about 5 mls (approximately a tablespoonful) of blood will be collected at months 6, 12, 18 & 24 to investigate how your child is building up malaria specific immunity. For these, your child will be asked to come to the study clinic even if he/she is not sick. The scheduled tests including the immunological tests are not part of standard clinical guidelines but are done for the purpose of the study. All study visits will take place at home with a visit taking approximately 30 minutes. You will be asked to come back to the clinic with your child when he/she is sick.
What are the possible risks for participating in this study?

The study staff will take every effort to protect your information and that of your child. However, the possible risk to your child would be experiencing of some pain when blood is being collected.

What are the benefits for participating in this study?
Apart from study procedures, the study participants will have access to some medical services at the study clinic throughout their participation in the study. A dedicated Clinical Officer will attend to study participants at any point they present to the clinic sick.

Does your child need to participate in the study?
Participation in the study is entirely voluntary. Even if you agree to participate, you may withdraw your child at any point in time. This will not affect the care that the child will receive at this hospital.

What will participating in the study cost me?
You will not pay anything for participating in this study and we will not pay you for taking part in the study. If you are asked by study staff to come to the study clinic, we will reimburse for the transport costs accordingly.

Who should I contact if I have a problem?
This study will be reviewed and approved by the College of Medicine Research and Ethics Committee (COMREC) and the Liverpool School of Tropical Medicine Ethics Committee. If you have any questions about your rights or the rights of your child for participating in this study, please, contact the chairman of the COMREC Prof. Mfutso-Bengo on telephone number 01871911. You may also contact the study Clinician Mr Zinenani Truwah on 0999413775.

Participant Agreement

I have understood the information contained in this consent form and I hereby voluntarily agree that my child participate in this study.

Name of child participating in the study		Date

Name of the person giving consent (guardian)	Signature	Date

Name of the person obtaining consent	Signature	Date

For illiterate guardians

Thumb Print of guardian

Name of Witness	Signature	Date

Appendix 14: Guiding questions for In-depth Interviews

Lived experiences of HIV infected women administering CPT to their HIV exposed, uninfected infants

Introduction

My name is _____. I will be asking you questions on cotrimoxazole prophylaxis that is given to your child. Please feel free to answer these questions. The answers you provide will help to improve the care that is given to HIV exposed children who are receiving cotrimoxazole prophylaxis/Bactrim. Your name will not be recorded on this sheet and therefore, no one will know who said what in these interviews.

1. Did you receive information on giving your child contrimoxazole? If yes, what kind of information did you receive? Who gave you the information? Where was the information given? How was the information given? How sufficient was the information? **(Probe on sources of counselling messages until they are exhausted)**
2. From the time you first got the information, how often do you get similar kind of information? **(Probe: where the information is given and by whom)**
3. Do you think that this information is important to you (explain) **(Probe: How they have used the information, what they have benefited or not benefited by using the information**)
4. How best would you like to get messages about adherence to cotrimoxazole prophylaxis? **(Probe: where the information should be provided, who should provide the information and how the information should be provided?)**
5. How are you reminded to give cotrimoxazole to your child? Who reminds you and how often do you get reminded?
6. What problems do you experience when using the approach you use to be reminded about giving cotrimoxazole to your child? How can these problems be addressed?
7. How would you like others help you (spouse, family members, community members, religious friends) as regards giving cotrimoxazole to your child?
8. How much support do you receive from family members as regards to giving your child cotrimoxazole prophylaxis?
9. What things would make you not give cotrimoxazole to your child? How would you deal with family members who do not know your HIV status?
10. How is it important or beneficial to give children cotrimoxazole prophylaxis? (Explain)
11. What makes you continue giving your child cotrimoxazole prophylaxis even after knowing your child is HIV negative at 6 weeks and/or your child is looking healthy? **(Probe for more reasons why mothers give cotrimoxazole to their children)**
12. What do you do when your child is sick and is receiving other forms of treatment i.e. too many other drugs for the sickness **(Probe to see if mothers stop giving cotrimoxazole when child is on other forms of treatment)**
13. Who makes decisions about health and care in your family? How do you think this may impact on giving your child cotrimoxazole on daily basis?
14. What aspects of your culture/tradition/religion/social norms encourage you continue giving cotrimoxazole to your child? **(Probe: tradition/religion/social norms/personal issues).** What aspect of your culture discourages you to continue providing cotrimoxazole to your child? **(Probe: tradition/religion/social norms/personal issues)**

15. What happens in terms of giving cotrimoxazole prophylaxis to your child when you are away from home like attending a funeral or you have travelled to another area where you will spend days?
16. What are your worries with giving your child cotrimoxazole on daily basis for a period of one year? How can these worries be addressed?
17. How can disclosure or non disclosure of your HIV status to your spouse or family members affect giving cotrimoxazole to your child (Explain)

Appendix 14: Guiding questions for Focus Group Discussions

Lived experiences of HIV infected women administering CPT to their HIV exposed, uninfected infants

What kind of information did you receive on giving your child cotrimoxazole? In what context was the information given? How was the information given to you? Where did you get this information? From the time you first got the information, how often to you get similar kind of information? Do you think that this information is important to you? (Explain) **(Moderator probe on sources of counseling messages on administering cotrimoxazole until they are exhausted)**

How best would you like to get messages about adherence to cotrimoxazole prophylaxis?

How are you reminded to give cotrimoxazole to your child? Who reminds you and how often do you get reminded? What problems do you experience when using the approach you use to be reminded about giving cotrimoxazole to your child?

How much support do you receive from family members as regards to giving your child cotrimoxazole prophylaxis?

What factors would make you not give cotrimoxazole to your child? How would you deal with family members who do not know your HIV status?

How would you like others help you (spouse, family members, community members, religion) as regards giving cotrimoxazole to your child?

What makes you continue giving your child cotrimoxazole prophylaxis even after knowing your child is HIV negative at 6 weeks and/or your child is looking healthy? **(Moderator probe for more reasons why mothers give cotrimoxazole to their children)**

What do you do when your child is sick and is receiving other form of treatment i.e. too many other drugs for the sickness **(Moderator probe to see if mothers stop giving cotrimoxazole when child is on other forms of treatment)**

Who makes decisions about health and care in your family? How do you think this may have any impact on giving your child cotrimoxazole on daily basis?

What aspects of your culture/tradition/religion/social norms encourage you to continue giving cotrimoxazole to your child? (**probe: tradition/religion/social norms/ personal issues**)What aspect of your culture discourages you to continue providing cotrimoxazole to your child? (**probe: tradition/religion/social norms/personal issues**)

What happens when you are away from home like attending a funeral or you have travelled to another area where you will spend days?

What are your worries with giving your child cotrimoxazole on daily basis for a period of one year? How can these worries be addressed?

How do you think disclosure or non-disclosure of your HIV status to your spouse or family members affect giving cotrimoxazole to your child?

Do you think you have all the support you need from family members in giving your child cotrimoxazole? How adequate is the support that you get from family members in giving your child cotrimoxazole? (Explain)