A STUDY TO DETERMINE THE MORBIDITY AND MORTALITY PATTERNS OF MALARIA IN CHILDREN IN A VERY LOW TRANSMISSION SETTING

By

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DECLARATION

I, **Patricia Mupeta Bobo**, hereby declare that this dissertation represents my own work and has not been presented either wholly or in part for a degree at the University of Zambia or any other university.

It has been produced in accordance with the guidelines for the Master of Medicine in Paediatrics and Child Health of the University of Zambia.

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CERTIFICATE OF APPROVAL

The University of Zambia approves this dissertation of Patricia Mupeta Bobo in partial fulfilment of the requirements for the award of the degree in Master of Paediatrics and Child Health.

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1. Name……………………...

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ABSTRACT

Background: Despite several strides made to control malaria in Zambia, it still is endemic in many parts of the country and remains one of the leading causes of morbidity and mortality. Its epidemiology is characterised by varying transmission intensities which may bring about change in the patterns of malaria morbidity and mortality.

Objective: To determine the patterns of malaria morbidity and mortality among children presenting to the University Teaching Hospital (UTH), Lusaka, Zambia, a very low malaria transmission zone.

Method: The study was conducted between November 2014 and August 2015. Residents of Lusaka aged 0 - 15 years with MPS or RDT confirmed malaria were enrolled. Their data on demographic characteristics, clinical presentation, laboratory and treatment outcomes were collected using a questionnaire and entered into EpiData and transferred into STATA statistical package version 12 for analysis.

Results: Total enrolled were 109 aged between 2 months to 15 years (median 5.6 years; inter quartile range [IQR] 3 – 8 years). The commonest symptom was fever at 94%. Proportions of uncomplicated and complicated malaria cases were 50.5% and 49.5%, respectively. History of travel was 54.6% among those with complicated and 45.4% with uncomplicated malaria. Infancy was not significantly associated with an increased risk of complicated malaria compared to ages 1-5years (OR 0.18, 95 CI: 0.02 – 1.67, p=0.13) and over 5 years (OR 0.18, 95 CI: 0.02 - 1.64, p=0.13). Children without history of travel were less likely to suffer from severe malarial anaemia compared to those who had (OR 1.65, 95 CI: 0.69 – 3.95, p=0.26). Infancy compared to ages 1-5 years (OR 0.64, 95 CI: 0.08 – 4.89, p=0.67) and above 5 years (OR 0.92, 95 CI: 0.13 – 6.38, p=0.93) and history of travel (OR 0.38, 95 CI: 0.12 – 1.25, p=0.17) were not significantly associated with increased risk of cerebral malaria. Four (3.7%) died, all without history of travel and all from cerebral malaria (CFR 21.1%).

Conclusion: Severe malarial anaemia was the commonest pattern of severe disease. Mortality was unexpectedly low in this cohort of children. There is need for similar studies to be done periodically to monitor changes overtime.

I dedicate this dissertation to my daughters, for their love and understanding while I was busy working on this, to my family and friends for their immeasurable support during the whole period of the programme, and to God, for his unending faithfulness.

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LIST OF ABBREVIATIONS

CCF	Congestive Cardiac Failure
CNS	Central Nervous System
ERES	Excellence in Research Ethics and Science
FBC	Full Blood Count
Hb	Haemoglobin
HIV	Human Immunodeficiency Virus
IQR	Inter quartile range
ITN	Insecticide Treated Mosquito Net
LFT	Liver Function Tests
MoH	Ministry of Health
NAI	Naturally Acquired Immunity
NMCP	National Malaria Control Programme
PICU	Paediatric Intensive Care Unit
RBS	Random Blood Sugar
RDT	Rapid Diagnostic Test
UTH	University Teaching Hospital
WHO	World Health Organisation

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CHAPTER 1

1. INTRODUCTION

Zambia, like the rest of the world, has identified malaria control as one of its main public health priorities, with the aim of sustaining the gains achieved during initial scale-up efforts of malaria control interventions which started around early 2000. This is also in line with the country's vision of achieving 'a malaria-free Zambia by 2030' (Ministry of Health [MOH], 2013). Data from 2001 to 2008 shows that there have been significant reductions in the malaria burden, demonstrated by a decline in in-patient malaria cases, over 60% decline in deaths due to malaria, and a decline in anemia attributable to malaria in under-five children (National Malaria Control Programme [NMCP], 2011).

Malaria, however, remains endemic in Zambia with seasonal and geographical epidemiological variations and remains one of the leading causes of morbidity and mortality as reported by the Demographic Health Survey of 2012/2014 (CSO, 2015). Indeed, there has been an upsurge in malaria cases and deaths observed in some provinces, particularly the Northern and Luapula provinces since 2009 (NMCP, 2011; Mukonka et al, 2014 and Nambozi et al, 2014).

Biemba and others (2000) conducted a study in Zambia at Macha Mission Hospital, where *P. falciparum* malaria was endemic at that time. Hospital records of 6 200 children up to six years of age admitted to the hospital between

1994 and 1996 found severe malarial anaemia in 590 children (9.5% of paediatric admissions) and strictly defined cerebral malaria in 286 children (4.6% of paediatric admissions). Ninety-eight (1.58%) of these patients had a combination of both complications. Severe malarial anaemia correlated strongly with the degree of parasitaemia, malnutrition indicated by low weight for age, absence of fever and late presentation in the malaria season. In contrast, patients with cerebral malaria were more often febrile and presented earlier in the malaria season. The case fatality rate (CFR) of severe malarial anaemia (8.8%) was about half that of cerebral malaria (18.9%), but because severe malarial anaemia was more common, these two forms of complicated malaria were implicated in similar numbers of in-hospital paediatric deaths (Biemba et al, 2000).

Currently and from epidemiological data of 2010, Zambia is divided into three malaria epidemiological zones. A zone is defined as an area reflective of the population-based survey estimates of malaria parasitemia among children under five years of age who represent approximately 20% of the total population (NMCP, 2011).

Zone 1 comprises areas where malaria control has markedly reduced transmission and parasite prevalence is less than 1% (Lusaka city and environs). *Zone 2* encompasses areas where sustained malaria prevention and control have markedly reduced   transmission and where parasite prevalence is between 1%

and 14% in young children at the peak of transmission (Central, Copperbelt, North-Western, Southern, and Western Provinces), while *Zone 3* comprises areas where progress in malaria control has been attained, but not sustained; where lapses in prevention coverage have led to resurgence of infection and illness; and where parasite prevalence in young children is 15% or more at the peak of the transmission season (Eastern, Luapula, Muchinga and Northern Provinces) [NMCP, 2011].

According to data from the Zambia National Malaria Indicator Surveys conducted by MOH through NMCP between 2006 and 2012, the malaria parasite prevalence, as measured by slide microscopy, and severe anaemia (haemoglobin [Hb] less than 8 g/dl) have changed quite dramatically across the surveys. Overall, malaria parasite prevalence, across the country, declined from 21.8% in 2006 to 10.2% in 2008, then rose to 16.0% in 2010, and stood at 14.9% in 2012. Severe malarial anaemia prevalence was 13.8%, 4.3%, 9.2% and 9.2% in 2006, 2008, and 2012, respectively (MOH, 2013). In children under the age of five years, the prevalence of malaria parasite was 22.1%,10.2%, 16%, and 14.9% in 2006, 2008, 2010 and 2012 respectively, and severe anaemia was 14%, 4%, 9% and 6.8% for the same period, respectively. Also noted is a shift in the peak of parasitaemia from age two years in 2006 to age four in 2012 (MOH, 2013).

Currently Lusaka Province generally, and Lusaka City and environs specifically, are in a very low transmission zone with relatively stable transmissions over the same period: 8%, 1.7%, 0.4% and 0.4% in 2006, 2008, 2010 and 2012 respectively, while severe anaemia has been 7.5%, 4.2%, 4.2% and 4.4% for the same period, respectively (MOH, 2013).

1.1. STATEMENT OF PROBLEM

Zambia, through various malaria control programmes, has reduced the prevalence of malaria parasitaemia country wide from 21.8% in 2006 to 14.9% in 2012, with significant variations occurring in different provinces (MOH, 2013). This change in malaria parasitaemia prevalence may bring about change in the pattern of morbidity of malaria (Snow and Marsh, 2002; Doolan et al, 2009). Current data already shows a shift in the peak of parasitaemia from age two years in 2006 to age four in 2012 (MOH, 2013), a change which is in line with changes reported elsewhere where reduction in transmissions have been noted (Snow et al, 1997; Reyburn et al, 2005; Idro et al, 2006; Okiro et al, 2009). Further, children may be less likely to develop adequate natural immunity against malaria due to inadequate exposure to the malaria parasites, and therefore be more prone to more severe malaria at a later stage (Snow and Marsh, 2002). Zambia might start experiencing increased morbidity and mortality in older children due to malaria as reported elsewhere (Snow and Marsh, 2002; Thomas et al, 2005; Okiro et al, 2009), particularly if the control

measures are not sustained and various parts of the country continue to experience an upsurge in malaria cases (MOH, 2013).

Little was known about the actual morbidity and mortality pattern of malaria in Lusaka city situated in a very low transmission zone.

1.2. STUDY JUSTIFICATION

The study sought to elucidate the patterns of malaria in a very low transmission setting such as Lusaka Province by studying the clinical features of children presenting with malaria to UTH, situated in Lusaka city. The elucidated clinical patterns of malaria morbidity and mortality, among children in a very low transmission area, provides current evidence that can be used for development of area-specific malaria case management protocols besides informing national policies of the ongoing national and regional malaria control and elimination strategies. Indeed, to our knowledge, this is the first study describing malaria disease morbidity and mortality among children presenting at an urban tertiary health facility in a very low malaria transmission zone.

1.3. RESEARCH QUESTION

What are the patterns of morbidity and mortality of malaria in children in the very low malaria transmission setting of Lusaka?

1.4. MAIN OBJECTIVE

The main objective of the study was to determine the patterns of morbidity and mortality of malaria in children presenting to the University Teaching Hospital

(UTH) Department of Paediatrics and Child Health, Lusaka Province, a very

low malaria transmission area.

1.4.1. <u>Specific Objectives</u>

The specific objectives were as follows:

1.4.1.1.   To describe the clinical manifestations of malaria in children 15

years and below presenting with malaria to the UTH Department of

Paediatrics and Child Health

1.4.1.2.   To determine the disease outcome among the studied population

at the institution.

CHAPTER 2

2. LITERATURE REVIEW

2.1. GENERAL INFORMATION

According to the World Health Organisation (WHO) World Malaria Report of 2013 (WHO, 2013), there has been a wide-scale reduction in malaria incidence and mortality as a result of a tremendous expansion in the financing and coverage of malaria control programmes since 2000. Malaria, however, remains a public health problem in many countries despite these changes with an estimated 207 million cases of malaria in 2012 and an estimated 627 000 deaths, with 90% of all malaria deaths having occurred in sub-Saharan Africa. Seventy seven percent of all of these deaths occurred in children under five, that is, an estimated 483 000 children or 1300 children every day, or one child almost every minute (WHO, 2013).

Malaria is caused by five species of parasite that affect humans, and all of these species belong to the genus *Plasmodium*: *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi*. Of these, *P. falciparum* and *P. vivax* are the most important.

The median pre-patent period (time from parasite inoculation to detectable parasitemia) for *P. falciparum* infection is 10 days (range 5–10 days), and the

median incubation period (time from parasite inoculation to development of symptoms) is 11 days (range 6–14 days). The incubation period may be significantly prolonged by the level of immunity acquired through previous exposures, by anti-malarial prophylaxis, or by prior partial treatment, which may mitigate, but not prevent the disease (Trampuz, et al 2003).

2.2. FORMS OF MALARIA

According to WHO (2010), malaria is divided into uncomplicated and complicated malaria based on clinical presentation.

2.2.1. <u>Uncomplicated Malaria</u>

Uncomplicated malaria is defined as symptomatic malaria without signs of severity or evidence (clinical or laboratory) of vital organ dysfunction. In settings where the risk of malaria is low, clinical diagnosis of uncomplicated malaria should be based on the possibility of exposure to malaria and a history of fever in the previous three days with no features of other severe diseases; in settings where the risk of malaria is high, clinical diagnosis should be based on a history of fever in the previous 24 hours and/or the presence of anaemia. In all settings, clinical suspicion of malaria should be confirmed with a parasitological diagnosis (WHO, 2010).

The majority of patients with uncomplicated malaria experience fever (greater than 92% of cases), chills (79%), headaches (70%), and diaphoresis (64%).

Other common symptoms include dizziness, malaise, myalgia, abdominal pain, nausea, vomiting, mild diarrhoea, and dry cough. Physical signs include fever, tachycardia, jaundice, pallor, orthostatic hypotension, hepatomegaly, and splenomegaly. Clinical examination in non-immune persons may be completely unremarkable, even without fever (Trampuz et al 2003; Kliegman et al, 2007).

2.2.2. <u>**Complicated Malaria**</u>

WHO (2010) describes specific syndromes of severe (complicated) malaria as follows:

- Cerebral malaria - impaired consciousness or unarousable coma, multiple convulsions – more than two episodes in 24 hours

- Pulmonary oedema   - Clinical (deep breathing, respiratory distress - acidotic breathing), and / or radiological findings such as patchy areas of increased opacity, diffuse interstitial opacities, and, rarely, lobar consolidation

- Circulatory collapse or shock, systolic blood pressure less than 70 mm Hg in adults and less than 50 mm Hg in children

- Acute renal failure - serum creatinine more than 265μmol/l.

- Severe anaemia, and/or bleeding - severe normocytic anaemia (Hb less than 5 g/dl, packed cell volume less than 15%) / abnormal spontaneous bleeding

- Metabolic Acidosis - plasma bicarbonate less than 15 mmol/l

- Hypoglycaemia - blood glucose less than 2.2 mmol/l or less than 40 mg/dl

- Clinical jaundice plus evidence of other vital organ dysfunction

- Haemoglobinuria

- Hyperparasitaemia (greater than 2% or 100 000/μl in low intensity transmission areas or greater than 5% or 250 000/μl in areas of high stable malaria transmission intensity)

- Hyperlactataemia (lactate greater than 5mmol/l).

2.3. FACTORS THAT PROTECT AGAINST MALARIA

There exists naturally acquired immunity (NAI) to *P. falciparum* which protects millions of people routinely exposed to *P. falciparum* infection from severe disease and death which is virtually 100% effective among heavily exposed adults, and is also responsible for conferring a similar immunity exceeding 90% effectiveness in exposed high-risk infants in sub-Saharan Africa (Doolan et al, 2009).

 In regions where the disease is holoendemic, most people are almost continuously infected by *P. falciparum* and the majority of infected adults rarely experience overt disease despite a population of parasites in their blood that would almost universally prove lethal to a malaria-naive visitor (Baird et al, 2002; Doolan et al, 2009). Infants and young children, occasionally, do not have NAI, which is also compromised in pregnant women, especially primigravidae,

and adults removed from their routine infections, at least temporarily. In naive individuals of any age, *P. falciparum* infection is almost always symptomatic, with clinical symptoms observed even at very low parasitemia levels. Routine exposure to holoendemic malaria protects a majority of individuals while killing a minority. Therefore, interventions that reduce exposure below a level capable of maintaining NAI to malaria, risk the possibility of catastrophic rebound; aggressive interventions that consider only that vulnerable minority risk compromising or eliminating the solid protection against severe malaria in the majority (Doolan et al, 2009).

A given amount of exposure is required for effective clinical immunity to develop. When infection rates are high, exposure early in life furnishes a child with an acquired resistance to the consequences of infection (Snow et al, 1997). Maternal NAI confers some protection in babies initially, until around 3 to 4 months of age (Snow et al, 1997; Doolan et al, 2009), after which they become susceptible to severe disease and death (Drakeley et al, 2005; Carneiro et al, 2010, Guillebaud et al, 2013). In areas of very-low-intensity transmission, the lack of development of immunity is balanced by the low frequency of infection, so disease rates will be low (Snow et al, 1997).

The risk of cerebral malaria increases with age in children two to four years old. Thereafter the frequency of clinical disease begins to diminish and the risk of mortality sharply decreases. The age of onset of this protection is somewhat

earlier with heavier transmission, but protection rarely occurs before the age of two years (Doolan et al, 2009).

From adolescence onwards, severe disease very rarely occurs. Mild clinical episodes may still be quite common. People having chronic, heavy, and largely uninterrupted exposure to infection develop and maintain a highly efficacious protection from severe disease at an age corresponding roughly with the onset of puberty (Baird et al, 2002).

Apart from NAI, other factors have been studied to offer some degree of protection against malaria by promoting practices that limit exposure to the vector that transmit the disease. In Ghana, one study found that compared to urban areas, rural residence was found to both increase the incidence rate of malaria among exposed children, and increased the probability of being exposed. Results from this study revealed that in one site, 34% of urban residents were estimated to be at no risk, compared to 3% of rural residents; in another site, 47% of urban residents and 13% of rural residents were estimated to be at no risk (Cairns et al, 2013).

The socioeconomic situation is significantly associated with malaria even in holoendemic rural areas where economic differences are not much pronounced (Krefis et al, 2010). In a study conducted in Ghana whose objective was to quantify household socioeconomic levels using principal component analyses

(PCA) to a set of indicator variables and to use a classification scheme for the multivariate analysis of children less than 15 years of age who presented with and without malaria to an outpatient department of a rural hospital, a total of 1,496 children presenting to the hospital were examined for malaria parasites and interviewed with a standardized questionnaire. The information of eleven indicators of the family's housing situation was reduced by PCA to a socioeconomic score, which was then classified into three socioeconomic status (poor, average and rich). Their influence on the malaria occurrence was analysed together with malaria risk co-factors, such as sex, parent's educational and ethnic background, number of children living in a household, applied malaria protection measures, place of residence and age of the child and the mother. The multivariate regression analysis demonstrated that the proportion of children with malaria decreased with increasing socioeconomic status as classified by PCA ($p<0.05$). Other independent factors for malaria risk were the use of malaria protection measures ($p<0.05$), the place of residence ($p<0.05$), and the age of the child ($p<0.05$).

2.4. EFFECTS OF MALARIA TRANSMISSION INTENSITY ON DISEASE PRESENTATION

Research has shown that with the reduction in transmission, there are changes observed in the presentation of malaria. Snow and Marsh (2002) have reported that with very low transmission intensity, all age groups are susceptible to severe malaria whereas with increasing transmission intensities, older children

and adults suffer less severe disease. With high transmission rates the majority of severe cases occur in infants under one year of age. This pattern reflects the increasingly rapid acquisition of immune responses that limit the life-threatening effects of malaria with increasing exposure to the parasite.

With high transmission, severe malarial anaemia dominates and cerebral malaria is rare. As one moves towards lower transmission rates, cerebral malaria accounts for an increasingly large proportion of cases. Although the population risk of severe disease falls with age, the risk of death at an individual level may rise with age after an initial fall from very high case fatality rates in children aged less than 6 months old (Snow and Marsh, 2002; Carneiro et al, 2010).

People living in holoendermic areas of malaria, despite having acquired adaptive immunity (NAI), still do suffer from malaria. A study done in Nigeria where people living in three communities chosen on the basis of their hyperendemicity to malaria were studied, revealed that of 143, 528 outpatients registered at health facilities during the period of study, 30.2% of the cases were actually attributed to malaria, with the annual mean malaria morbidity rate reported to be 52.8% of total facility attendance. However, the symptoms were generally mild and included headache, fever, chills and joint pains. Splenomegally, anemia and cerebral malaria were the most severe morbidity indicators reported. There were no significant differences in the patterns of malaria transmission and morbidity rates among the communities (Chukwuocha and Dozie, 2011).

Locally here in Zambia, in an earlier alluded to study, Biemba et al (2000) reported similar patterns of malaria disease morbidity and mortality in Macha, at that time a malaria holoendemic rural area, with severe malarial anaemia in the studied children predominating at about twice the cases of cerebral malaria.

However, when study participants are drawn from areas that differ in malaria transmission rates, studies reveal differences in incidences and generally agree about the differences in malaria patterns observed as well as differences in factors such as age at risk and case fatality rates. An example is a prospective study that was done in The Gambia and Kenya where communities where followed up between three to five years by Snow and others (1997). They recorded paediatric admissions with severe malaria over this period from five discrete communities in the 2 countries. Demographic analysis of the communities exposed to disease risk allowed the estimation of age-specific rates for severe malaria. Within each community the exposure to *P. falciparum* infection was determined through repeated parasitological and serological surveys among children and infants. The presence of acute respiratory-tract infections (ARI) was used as a comparison.

Overall, 3 556 malaria admissions were recorded for the five sites. Forty-five to 52% of all admissions of children aged from one month up to the 10th birthday were due to malaria in communities of low malarial transmission settings compared to only 12% of admissions for a high malarial setting. The odds ratio

of the low-to-moderate transmission communities compared to the high transmission communities was 1·49 (95% CI 1·41 - 1·61). The risks of severe disease in childhood were lowest among populations with the highest transmission intensities, and the highest disease risks were observed among populations exposed to low-to-moderate intensities of transmission. Similar trends were noted for cerebral malaria and for severe malaria anaemia but not for ARI. The changes in the rates of cerebral malaria showed a significant decline with increasing transmission intensity from low-to-moderate to high (OR 3·86 [2·86—5·47]). Mean age of disease decreased with increasing transmission intensity: from 49 months in a low transmission setting to 17 months in a high transmission setting. At the most intense levels of transmission the risk of severe disease was greatest during the first two years of life; after that risk fell rapidly (Snow et al, 1997).

In Kenya, a study conducted among school going children in two areas that differ in intensity of transmission showed a six-fold higher incidence of malaria attacks in children living in an area of low transmission, compared with school children living in a holoendemic area with intense perennial transmission during the same period. The authors concluded that malaria morbidity among school age children increases as transmission intensity decreases (Clarke et al, 2004).

A similar study described the clinical manifestations and case fatality of severe *P. falciparum* malaria at varying altitudes resulting in varying levels of

transmission. A total of 1 984 patients admitted for severe malaria to 10 hospitals serving populations living at levels of transmission varying from very low (altitude greater than1200 m) to very high (altitude less than 600m) in a defined area of northeastern Tanzania between February 2002 to February 2003 were followed up. Their results revealed as follows: the median age of patients was one year in high transmission, three years in moderate transmission, and five years in low transmission areas. The odds of severe malarial anemia (hemoglobin less than5 g/dL) peaked at one year of age at high transmission and at two years at moderate and low transmission intensities and then decreased with increasing age (P = .002). Odds were highest in infants (0-1 year: referent; 2-4 years: odds ratio [OR], 0.83; 95% confidence interval [CI], 0.72-0.96), 5 to less than15 years: OR, 0.44; 95% CI, 0.27-0.72; greater than or =15 years: OR, 0.44; 95% CI, 0.27-0.73; P less than0.001) and high transmission intensity areas (altitude less than 600m: referent; 600m to 1200m: OR, 0.55; 95% CI, 0.35-0.84; greater than 1200m: OR, 0.55; 95% CI, 0.26-1.15; P for trend = .03). The odds of cerebral malaria were significantly higher in low transmission intensity areas (altitude of residence less than 600m: referent; 600m to 1200m: OR, 3.17; 95% CI, 1.32-7.60; greater than1200m: OR, 3.76; 95% CI, 1.96-7.18; P for trend = .003) and with age 5 years and older (0-1 year: referent; 2-4 years: OR, 1.57; 95% CI, 0.82-2.99; 5 to less than15 years: OR, 6.07; 95% CI, 2.98-12.38; greater than or =15 years: OR, 6.24; 95% CI, 3.47-11.21; P less than 0.001). The overall case-fatality rate of 7% (139 deaths) was similar at high and moderate levels of transmission but increased to 13% in low transmission areas (P = 0

17

.03), an increase explained by the increase in the proportion of cases with cerebral malaria. The study concluded that age and level of exposure independently influenced the clinical presentation of severe malaria and that an increase in the proportion of cases with more fatal manifestations of severe malaria was likely to occur only after transmission has been reduced to low levels where the overall incidence is likely to be low (Reyburn et al, 2005).

In another study done in Tanzania focusing on the age patterns of severe paediatric malaria and their relationship to *P. falciparum* transmission intensity, admission data of children aged 0-9 years admitted to hospital were assembled from 13 hospitals serving 17 communities between 1990 and 2007). The analysis focused on the relationships between community derived parasite prevalence and the age and clinical presentation of paediatric malaria. Results revealed that as transmission intensity declined a greater proportion of malaria admissions were in older children. There was a strong linear relationship between increasing transmission intensity and the proportion of paediatric malaria admissions that were infants ($R^2 = 0.73$, p less than 0.001). Cerebral malaria was reported among 4% and severe malaria anaemia among 17% of all malaria admissions. At higher transmission intensity cerebral malaria was a less common presentation compared to lower transmission sites. There was no obvious relationship between the proportions of children with severe malaria anaemia and transmission intensity (Okiro et al, 2009).

In a study conducted in a tertiary hospital situated in an area of high malaria transmission in India, the mean age recruited with severe malaria was five years old. The CFR due to cerebral malaria and severe malaria was, respectively, 32% and 9% among PCR confirmed mono P.*falciparum* cases with the peak morbidity and mortality in younger children regardless of seasonality (2014 Jain et al).

A study done in Uganda found somewhat conflicting results to the studies above in regards cerebral malaria and the transmission intensity. This study looked at how the peripheral parasite load varies with transmission intensity and how this influences the symptoms and manifestations of severe malaria in children under five years in three areas with different malaria transmission intensity across Uganda. Six hundred and seventeen children with severe malaria presenting to three hospitals in areas with very low (51), moderate (367) and very high (199) transmission intensities were recruited (Idro et al, 2006). The findings revealed that the median age (months) was inversely proportional to transmission intensity and declined with rising transmission (26.4 in very low, 18.0 in moderate and 9.0 under very high transmission), and this was in keeping to many of the studies already described. The proportion of patients with seizures (13.7%, 36.8% and 45.7%, *P* less than 0.001) from very low, moderate and very high transmission respectively, increased with rising transmission. A linear increase with transmission was also observed in the proportion of those with repeated seizures (9.8%, 13.4% and 30.2%, *P* less than 0.001) or impaired

consciousness (7.8%, 12.8% and 18.1%, $P = 0.029$) but not respiratory distress.

The proportion of patients with severe anaemia (19.6%, 24.8% and 37.7%,

$P = 0.002$) mirrored that of patients with seizures (Idro et al, 2006). The findings

on anaemia are in keeping with the results as described by many of the other

results in studies already discussed above.

In areas of very low transmission rates, malaria outbreaks sometimes occur and

various factors are associated with these. Chaparro et al (2013) conducted a

study in Colombia following an outbreak of malaria in the country in 2010.

Their findings revealed that a greater incidence was found in men (65%) than in

women (35%) and that although about a third of cases occurred in children less

than 15 years of age, most of these cases occurred in children above the age of

five years. There were also some significant findings in regards to the ethnicity

of the cases with the least affected being the indigenous of the communities

studied as opposed to visitors and non-indigenous people.

In Senegal a malaria case investigation programme was piloted for 12 weeks in

2012 in Richard Toll district of northern Senegal, which is an area of very low

transmission. Malaria infections (N = 110) were identified through facility-based

passive case detection and investigated within three days. Rapid diagnostic tests

(RDT) and a brief questionnaire were administered to 5 520 individuals living

within the index case compound or within five neighbouring compounds.

Results revealed that in comparison with family and neighbours, index cases

were more likely to be male, age 15–49, and to report travel within the past 15 days that entailed an overnight stay. Twenty-three (0.4%) of family/neighbours were RDT-positive. Potential risk factors for infection among family and neighbours were examined, including: sex, age, occupation, travel history, bed net usage, and residence (index *vs* neighbouring compound). Adjusting for all factors, relative risk (RR) of infection was associated with residence in the index case household (RR = 3.18, p less than 0.05) and recent travel, including travel to Dakar, an area of high transmission (RR = 19.93, p less than 0.001), travel within the region (RR = 9.57, p less than 0.01), and to other regions in Senegal (RR = 94.30, p less than 0.001). Recent fever among RDT-positive family/neighbours was uncommon (30%). From this study the authors concluded that the primary risk factor for malaria infection in the low transmission district of Richard Toll is travel (Littrell et al, 2013).

A descriptive study of malaria cases in a general hospital in Madrid, Spain, carried out between 1996 and 2011 revealed 103 cases of malaria in children under 14 years old. Sixty percent were males and the average age was 4.5 years. In most cases, the infection arose during a visit to relatives in the country of origin. The vast majority did not have malaria prophylaxis. Twenty-five percent of the cases were diagnosed as complicated malaria, the main criteria being Hyperparasitaemia, of which 80% of the patients did not present any other complications (Paredes et al, 2013).

Another study that brings out the issue of travel as a risk factor for infection was an unmatched case–control study conducted among 560 adult patients at a health centre in central Ethiopia. Patients who received a malaria test were interviewed regarding their recent travel histories. Bivariate and multivariate analyses were conducted to determine if reported travel outside of the home village within the last month was related to malaria infection status. After adjusting for several known confounding factors, travel away from the home village in the last 30 days was a statistically significant risk factor for infection with *P. falciparum* (AOR 1.76; p=0.03) but not for infection with Plasmodium vivax (AOR 1.17; p=0.62). Male sex was strongly associated with any malaria infection [AOR 2.00; p=0.001] (Yukich et al, 2013).

These cited studies with their respective and varying results of malaria disease morbidity and mortality in various transmission settings, especially among the most vulnerable populations - the children, thus underscore the importance of regular elucidation of malaria disease patterns so as to inform policy for effective national disease control and case management, hence the need to have conducted the current study being reported here.

CHAPTER 3

3. RESEARCH METHODOLOGY

3.1. STUDY DESIGN

   This was a cross sectional study

3.2. STUDY SITE

The study was conducted in the Outpatient / Emergency unit of the UTH, Department of Paediatrics and Child Health which comprises three wards namely Ward A01 (Emergency Room) , Admission Ward, and Paediatric Intensive Care Unit (PICU). Ward A01 is the main port of entry of paediatric patients coming from outside the hospital with various medical problems, and from there they are either sent to PICU (critically ill patients needing intensive care) or Admission ward before they are reviewed again and assigned in-patient wards or discharged. Those who are considered fit to go home immediately are sent home upon being attended to in A01.

UTH is located in the capital city of Lusaka, an area of very low transmission setting according to MOH (2013). It is the largest referral hospital in Zambia.

In 2012 and 2013, a total of 16, 564 and 16, 191 children, respectively, were attended to, with the majority coming from within the city of Lusaka (UTH records, 2014). In 2012, 4.6% of the children attended to had malaria and so did 4.7% attended to in 2013.

3.3. STUDY POPULATION

3.3.1. <u>Inclusion Criteria</u>

- Children aged between 0 and 15 years presenting to the UTH Department of Paediatrics and Child Health in whom a diagnosis of malaria was made with a positive rapid diagnostic test (RDT) for malaria or malaria parasite slide (MPS).

- Children who had resided in Lusaka city and environs (bordering Kafue district to the South, Chibombo district to the north, Chongwe to the east and Mumbwa to the west, see map of Lusaka City [Figure 1] below), for the last one year or more, for those older than one year of age, or whose parents had resided in Lusaka City for over a year for those less than one year of age, were eligible for inclusion in the study. (The proposal was written and approved before Chilanga was given district status, hence for the purpose of this study it was still part of Lusaka City.)

3.3.2. <u>Exclusion Criteria</u>

Children diagnosed with malaria who normally reside outside Lusaka city or had been living outside Lusaka and environs for over one year as well as those whose parents/guardians refused to give consent to participate in the study.

3.4. SAMPLING

Convenient sampling was used and patients were included as they were attended to in the Emergency Unit until the sample size was reached.

3.5. SAMPLE SIZE

Sample size was calculated using OpenEpi, Version 2, open source calculator (Openepi, 2014) with the following assumptions made:

- The number of paediatric patients seen at UTH/year is 16, 377 (average for 2012 and 2013).

- The proportion of cases of malaria among children seen at UTH remained almost steady at 4.6% in 2012, and 4.7 percent in 2013. Therefore 4.7% was used as an estimate of the prevalence of malaria in children seen at UTH, and used in the calculation as shown below:

Calculation:

$$N = \frac{Z^2 \times p\,(1-p)}{d^2} = \frac{1.96^2 \times 0.047\,(1-0.047)}{(0.04)^2} = 107$$

N=Sample size

Z=Z statistic (usually 1.96), at 95% percent confidence

3.6. STUDY PROCEDURES

The study was conducted between November 2014 and August 2015. Prior to the onset of the study all doctors and nurses working in the Emergency unit had been asked to alert the principal investigator (PI) or any of the study nurses

every time they came across a patient with malaria. The PI also worked in Ward A01 during various designated shifts, as well as during her spare time to enrol patients in the study.

Upon opening a file from the reception, children were taken into the nurses' bay for measurement of anthropometric measurements (weights, height and MUAC for the under five children) and temperatures before being sent to the emergency room (Ward A01) where they were attended to by a doctor. Those with suspected malaria were tested with an RDT and/ or malaria parasite slide (MPS). Those who tested positive were further subjected to other routine tests: approximately 5ml of blood was collected for a full blood count (FBC), and liver and renal function tests and the samples were taken to the UTH laboratory located within the department. Urinalysis was also done as part of routine physical examination as well as a needle prick for random blood sugar (RBS). All children were then offered an HIV test by UTH counsellors as per hospital routine procedures and their results put on their files using special stickers for confidentiality. Treatment was instituted as per hospital guidelines on management. Once laboratory results were ready, they were also put on the patients' file.

The PI or the study nurses would then approach the patients and their caregivers and after explaining the details of the study to them, would invite them to participate if they met the inclusion criteria. Those who accepted were then asked to sign the consent (and sometimes assent) form.

The PI or study nurse thereafter administered the questionnaire based on

information directly from the care-giver and/or participant, as well as from the

results of their physical and laboratory results from the file. Those who were

admitted had their files reviewed upon discharge or death to complete the

questionnaire. The data was then entered into Epidata I 2000 software and later

analysed using STATA version 12.
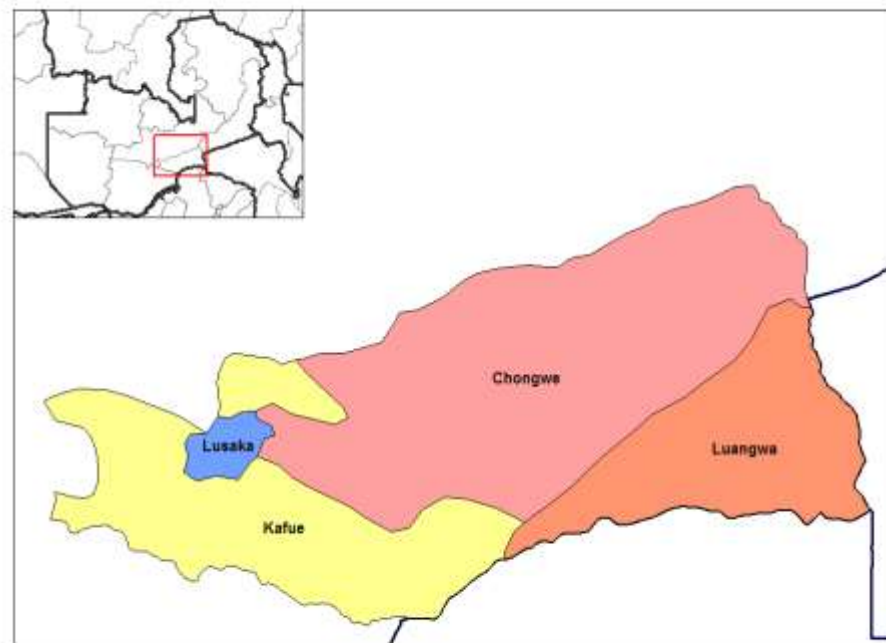
Figure 1: Map of Lusaka City (source: google maps, 2016)

3.7. DATA ANALYSIS

Data was entered into EpiData version 3.1 software database and then

transferred into STATA statistical package version 12 for analysis. Frequencies,

medians and percentages were used to describe the study population and the

outcomes. Chi-square tests were used to determine the association between

categorical variables (gender, age groups, HIV status, and nutritional status) and the outcomes. Odds ratio was used as the measure of the association between the stated exposure variable and the outcomes.

3.8. ETHICAL ISSUES

Approval was sought from ERES Converge IRB and the UTH Department of Paediatric and Child Health. The respondents were informed of their right to take part in the study and informed consent obtained from the parents or care givers of the respective respondents before enrolling them to the study.

Assurances were given that all information provided by the respondents would be treated with utmost confidentiality. Respondents were availed with information regarding the authority they had to quit the study any time and to submit their complaints to the researcher and other relevant authorities. The consent forms were translated in both Nyanja and Bemba, the languages commonly spoken in the city of Lusaka. For those parents/guardians who could neither read nor write, the consent was read for them and they were asked to thumb print if they agreed to take part in the study.

CHAPTER 4

4. RESULTS

4.1. SOCIO-DEMOGRAPHIC DATA

4.1.1. <u>Background Information</u>

During the study period, November 2014 to August 2015, 26, 531sick children with various other ailments were seen in the outpatient wards of the department. A of total 245 with confirmed malaria were diagnosed, out of which 151 were screened for enrollment into the study. The highest number of patients was recruited between January and July, with a peak around February (Graph 1 below). The peak of the malaria cases coincided with the peak of the two most commonly seen patterns of malaria severity, severe anaemia malaria and cerebral malaria. Severe anaemia malaria had another peak between June and July.
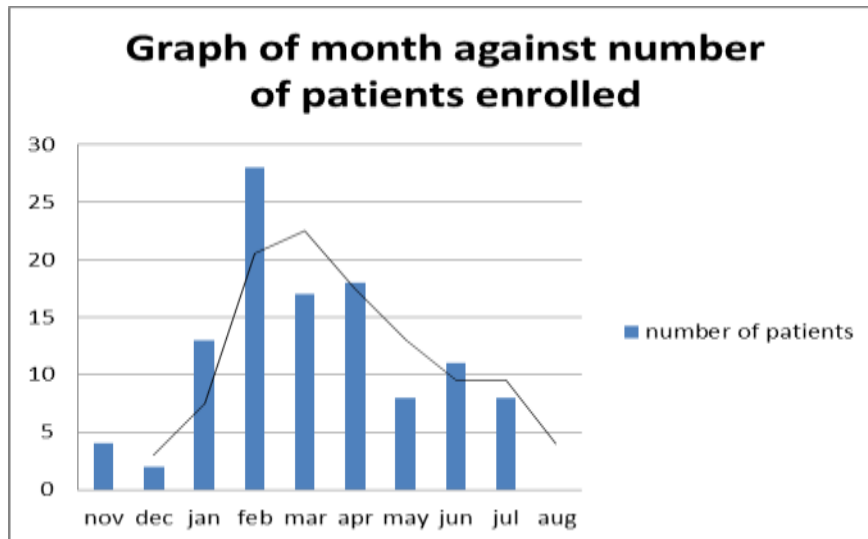
Graph1: Graph of month against number of patients enrolled

Of the 151 screened cases, 109 were eligible and they all consented and were enrolled in the study and the data collected analyzed (figure 2).
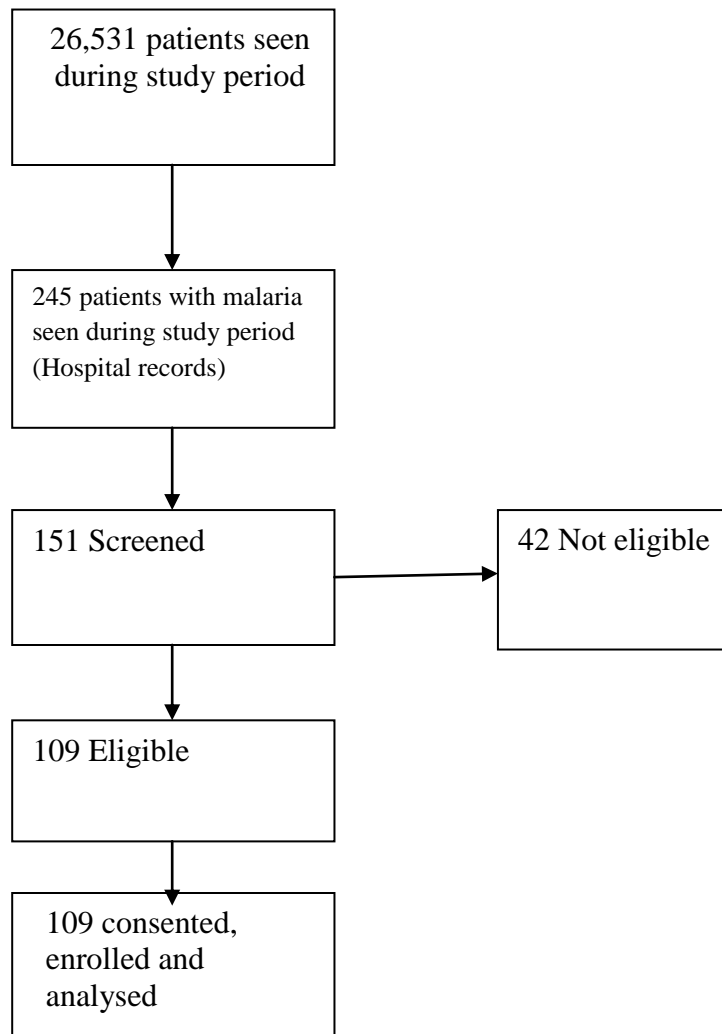
Figure 2: Flow diagram of cross-sectional survey

4.1.2. Background Information

Table 1 below gives a summary of some of the characteristics of the study

population. The prevalence of malaria among sick children seen at UTH's

department of Paediatrics and Child Health during the study period was

0.9%. The ages of the participants ranged between two months and 15

years, with the median age of 5.6 years, inter quartile range (IQR) [3 – 8

years]. Sixty five (60%) of the participants were male and 44 (40%)

female. Overall, infants were 6 (5.5%), 42 (38.5%) were between one and five years, and those over five years were 61 (56.0%).

The ages of the male participants ranged from three months to 14 years, with a median of 5.2years, IQR [2 – 7 years]. For the females, the ages ranged between two months to 15 years, with a median of 6.2 years, IQR [3 – 9 years]. The total number of under five children was 48 (44.0%) with a median age in months of 33.0, IQR [23 – 46 months]. The males ranged from three to 59 months, IQR [23 – 45 months], and two to 56 months for females, IQR [24 – 47 months].

Eighty (73.4%) participants were residents of high density areas, 22 (20.2%) were from medium density areas, and 7 (6.4%) were from low density areas.

Forty-two (38.5%) participants owned insecticide treated mosquito nets (ITNs), 23 (35.4%) of males and 19 (43.2%) of the females; with even fewer actually using them [30 (71.4%), 16 (38.1%) and 14 (33.3%) males and females, respectively].

History of travel to a location outside Lusaka City was positive in 66 (60.5%), 41 (63.1%) males and 25 (56.8%) females. The Copperbelt Province was visited by16 (24.2%); 11(16.9%) males and 5 (11.4%)

females, Eastern Province by 13 (19.7%), 11 (16.7%) visited Central

Province, 10 (15.4%) males and 1 (2.3%) female.

The history of having received a visitor from outside Lusaka was positive

in only 6 (5.5%).

4.1.3. Clinical Features

Most children presented with fever (103 [94.5%]), followed by loss of

appetite (50 [45.9%]), vomiting and headache (43 [39.5%] each,

respectively) and seizures (42 [38.5%]). Cough was seen among 25

(22.9%), diarrhoea among 18 (16.5%) and yellowing of eyes (8 [7.3%]).

The one child (0.9%) who presented with urinary symptoms (proteinuria)

was a known patient with End Stage Kidney Disease (ESKD), the other

urinalysis performed (83[76.1%]) were essentially normal.

Random Blood Sugar (RBS) ranged from 0.6mmol/L – 12mmol/L with a

mean of 6.0 (SD 2.0).

Splenomegaly alone was found in 5 (4.6%) of the participants, and in

combination with hepatomegaly (hepatosplenomegaly) in 9 (8.3%).

The platelet count ranged from 2 x 10^9/L to 880 x 10^9/L, with a mean of

140.0 x 10^9/L (SD 129.3). None of the children with severe

thrombocytopenia had any signs and symptoms of bleeding.

The nutritional status of 14 of the 48 under 5 children (29.2%) was less than minus 2 (z score <-2), 8 (16.7%) was z score <-1, and 26 (54.2%) was around the median z score.

Of the study population, only 4 (3.7%) were HIV positive.

Seven (6.4%) of the children had other co-morbidities other than HIV, with typhoid topping the list with 3 (2.8%) participants, one male (1.5%) and 2 (4.5%) females. The other co-morbidities that were present were asthma, pneumonia, worm infestation and End Stage Kidney Disease (ESKD), and these were found in one child each (0.9%), respectively.

Table1: Socio-demographic characteristics of the 109 study participants

VARIABLE	MALE	FEMALE	TOTAL
Study population (All) [%]	65 (59.6)	44 (40.4)	109 (100)
Age			
all (years) **Mean (SD)**	5.2 (3.5)	6.2 (4.1)	5.6 (3.8)
under 5s (months) **Mean (SD)**	33.1 (16.6)	32.8 (16.6)	33.0 (16.2)
<1 year (%)	4 (66.7)	2 (33.3)	6 (5.5)
1 – 5 years (%)	26 (61.9)	16 (38.1)	42 (38.5)
>5 years (%)	35 (57.4)	26 (42.6)	61 (56.0)

Residence			
high density (%)	47 (72.3)	33 (75.0)	80 (73.4)
medium density (%)	13 (20.0)	9 (20.4)	22 (20.2)
low density (%)	5 (7.7)	2 (4.5)	7 (6.4)
HIV Status			
Positive (%)	3 (4.6)	1 (2.3)	4 (3.7)
Negative (%)	61 (93.8)	41 (93.2)	102 (93.6)
Unknown (%)	1 (1.5)	2 (4.5)	3 (2.8)
ITN ownership			
no	42 (64.6)	25 (58.8)	67 (61.5)
yes	23 (35.4)	19 (43.2)	42 (38.5)
ITN use			
no (%)	7 (16.7)	5 (11.9)	12 (28.6)
yes (%)	16 (38.1)	14 (33.3)	30 (71.4)
History of Travel			
no (%)	24 (36.9)	19 (43.2)	43 (39.4)
yes (%)	41 (63.1)	25 (56.8)	66 (60.5)
Travelled to (Province)			
Copperbelt (%)	11 (16.9)	5 (11.4)	16 (24.2)
Eastern (%)	6 (9.2)	7 (10.6)	13 (19.7)
Central (%)	10 (15.4)	1 (2.3)	11 (16.7)
Other (%)	14 (7.7)	12 (4.5)	26 39.4)

4.2. SPECTRUM OF MALARIA SEVERITY

Table 2 below shows the malaria severity in various categories of the study population. Of the 109 participants, 55(50.5%) had uncomplicated malaria, 34 (52.3%) of the males and 21 (47.7%) of the females. The remaining 54 (49.5%) had complicated malaria (31 [47.7%] of the males and 23 [52.3%] of the females). Males were less likely than females to have complicated malaria compared to uncomplicated malaria (OR 1.2. 95 CI: 0.6 – 2.6). This was however not statistically significant (p=0.64).

Of the six infants with malaria, 5 (83.3%) had complicated malaria. Among children between one and five years of age, 22 (52.4%) had uncomplicated malaria while 20 (47.6%) had complicated malaria. In children over five years, 32 (52.5%) had uncomplicated and 29 (47.5%) had complicated malaria. Children under one year of age were thus more likely to have complicated malaria compared to those in the age groups 1-5years (OR 0.18, 95 CI: 0.02 – 1.67, p=0.13) and also those over 5 years (OR 0.18, 95 CI: 0.02 - 1.640, p=0.13). This association was not statistically significant.

In terms of area of residence, a diagnosis of uncomplicated malaria was made in 42 (52.5%) from high density areas, 10 (45.4%) were from medium density areas and 3 (42.9%) children were from low density areas. Thirty-eight (47.5%) from high density areas, 12 (54.6%) from medium density areas and 4 (57.1%) from low density areas had complicated malaria.

Children from high density areas were therefore less likely to have complicated malaria compared to those from medium (OR 1.33, 95 CI: 0.51 – 3.42); and those from low density areas (OR 1.47, 95 CI: 0.31 – 7.01). This was however not statistically significant (p=0.56 and p=0.63, respectively).

Of the children with uncomplicated malaria, 25 (58.1%) had no history of travel outside Lusaka city, while 30 (45.4%) had a positive history of travel. Among those with complicated malaria, 18 (41.9%) had no history of travel outside Lusaka while 36 (54.6%) had history of travel. From this, children with no history of travel to areas outside Lusaka city were less likely to have complicated malaria compared to those with history of travel (OR 1.7. 95 CI: 0.8 – 3.6). This was not statistically significant (p = 1.68).

Table 2: Spectrum of Malaria Severity

Variable	Types of Malaria		OR	CI	p-value
	Uncomplicated	Complicated			
Sex					
male (%)	34 (52.3)	31 (47.7)	-	-	-

female (%)	21 (47.7)	23 (52.3)	1.20	0.56, 2.58	0.64
Total (%)	55 (50.5)	54 (49.5)			
Age category					
<1 year (%)	1 (16.7)	5 (83.3)	-	-	-
1 – 5 years (%)	22 (52.4)	20 (47.5)	0.18	0.02, 1.67	0.13
>5 years (%)	32 (52.5)	29 (47.5)	0.18	0.02, 1.64	0.13
Residence					
high density (%)	42 (52.5)	38 (47.5)	-	-	-
medium density (%)	10 (45.4)	12 (54.6)	1.33	0.51, 3.42	0.56
low density (%)	3 (42.9)	4 (57.1)	1.47	0.31, 7.01	0.63
Travel history					
no	25 (58.1)	18 (41.9)			
yes	30 (45.4)	36 (54.6)	1.57	0.77, 3.62	1.68

4.3. PATTERN OF COMPLICATED MALARIA

Fifty four (49.5%) of the children in the study had complicated malaria. The

graph below shows the pattern of complicated malaria. The commonest form of

complicated malaria was severe anaemia [32 (59.3%)], followed by cerebral

malaria [19 (35.2%)], and lastly hypoglycaemia (3 [5.5%]). These are further described in tables 3a, 3b and 3c, respectively.
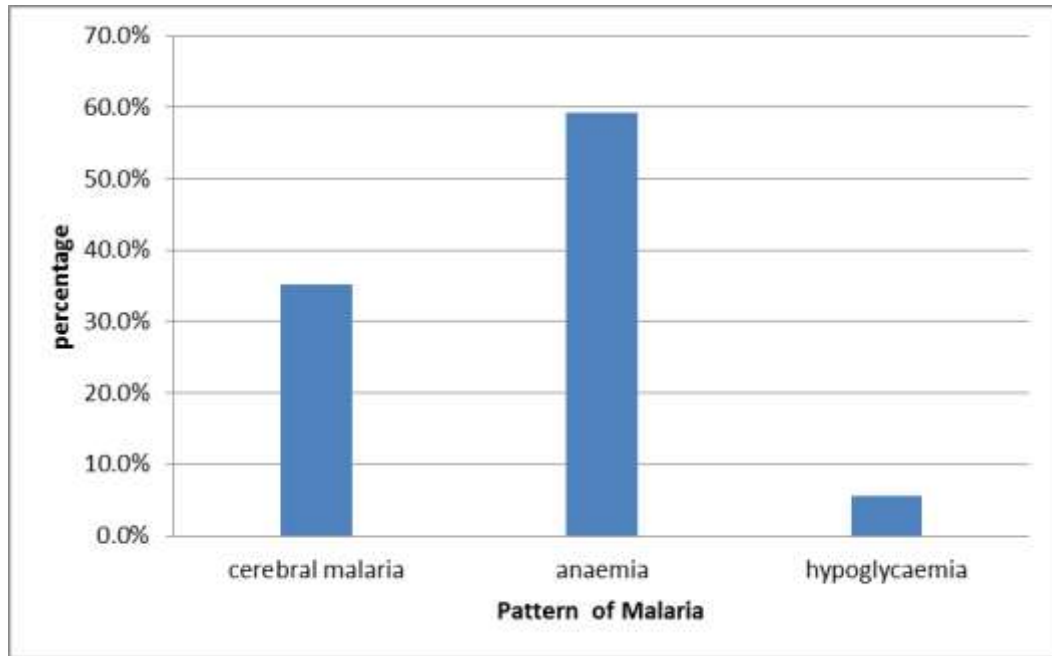
Graph 2: pattern of severe malaria

4.3.1. <u>Severe Anaemia</u>

The mean haemoglobin (Hb) was 7.2mg/dl (SD 3.0). The Hb ranged between 1.4mg/dl and 14.5mg/dl.

Pallor was observed in 76 (69.7%) of all patients, including 7 (6.4%) of patients with an Hb 10g/dl and above (One child reported clinically pale had an Hb of 13.3g/dl).

Clinically, congestive cardiac failure (CCF) as a complication of severe anaemia defined as severe anaemia, either clinical or laboratory, with

hepatomegaly with or without oedema, was diagnosed in half of the children (50%) with severe anaemia. Eleven (10.1%) of patients were males, and 5 (4.6%) were female, with no statistical significance (p=0.36). One (0.9%) under the age of one year, 5 (4.6%) between 1 – 5 years and 10 (9.2%) had CCF, and this was statistically significant (p=0.04). Thirteen (11.9%) of these children were from high density areas and 3 (2.8%) were from medium density areas, and this was statistically significant (p=0.04). Five (4.6%) and 11 (10.1%) had history of travel and this was not statistically significant (p=0.09).

Forty-three (39.4%) received blood transfusions as part of their management.

Table 3a below shows that males were less likely than females to have malaria with severe anaemia (OR 1.22, 95 CI: 0.53 – 2.81). This association was not statistically significant (p=0.64).

Infants were more likely to have malaria with severe anaemia compared to those between 1 – 5 years (OR 0.45, 95 CI: 0.08 – 1.94), and compared to those over 5 years (OR 0.36, 95 CI: 0.07 –1.94). Both these associations were not statistically significant (p=0.36 and p=0.23, respectively).

Those with no history of travel were less likely to suffer from malaria with severe anaemia compared to those who had history of travel (OR 1.65, 95 CI: 0.69 – 3.95), though this association had no statistical significance (p=0.26).

Table 3a: Pattern of Complicated Malaria – Severe anaemia

Variable	Severe anaemia		OR	CI	p-value
	No	Yes			
Sex					
male (%)	47(72.3)	18(27.7)			
female (%)	30(68.2)	14(31.8)	1.22	0.53, 2.81	0.64
Total (%)	77(70.6)	32(29.4)			
Age					
<1 yr (%)	3(50)	3(50)			
1 – 5 yrs (%)	29(69.0)	13(31.0)	0.45	0.07, 2.53	0.36
>5yrs (%)	45(73.8)	16(26.2)	0.36	0.07, 1.694	0.23
Travel					
no (%)	33(76.7)	10(23.3)			
yes (%)	44(66.7)	22(33.3)	1.65	0.69, 3.95	0.26

4.3.2. <u>Cerebral Malaria</u>

Overall, 19 (17.4%) were diagnosed with cerebral malaria as defined by WHO (2010). Seizures were the commonest central nervous system (CNS) manifestation in 13 (68.4%) children, followed by altered levels of consciousness [7 (6.4%)]; confusion (4 [3.7%]), and unresponsiveness (unconsciousness) among 3 (2.8%).

As shown in table 3b, males were less likely than females to have cerebral malaria (OR 0.97, 95 CI: 0.31 – 3.00). This was however not statistically significant (p=0.96).

Infants were more likely to have cerebral malaria compared to those between 1 – 5 years (OR 0.64, 95 CI: 0.08 – 4.89), and those over five years (OR 0.92, 95 CI: 0.13 –6.38). Both these associations were not statistically significant (p=0.67 and p=0. 93, respectively).

Those with no history of travel were more likely to suffer from cerebral malaria compared to those who had history of travel (OR 0.38, 95 CI: 0.12 – 1.25). This was however not statistically significant (p=0.17).

Table 3b: Pattern of Complicated Malaria – Cerebral malaria

Variable	Cerebral malaria		OR	CI	p-value
	No	Yes			
Sex					

Variable	No (%)	Yes (%)			
male (%)	54(83.1)	11(16.9)			
female (%)	36(81.8)	8(18.2)	0.97	0.31, 3.00	0.96
Total (%)	90(82.6)	19(17.4)			
Age					
<1 yr (%)	4(66.7)	2(33.3)	-	-	-
1 – 5 years (%)	36(85.7)	6(14.3)	0.64	0.08, 4.89	0.67
>5yrs (%)	50(82.0)	11(18)	0.92	0.13, 6.38	0.93
Travel					
no (%)	34(79.1)	9(20.9)			
yes (%)	56(84.8)	10(15.2)	0.38	0.12, 1.25	0.11

4.3.3. <u>Severe Malaria with Hypoglycaemia</u>

The mean random blood sugar was 5.98mmol/l (SD 1.99), ranging between 0.6mmol/l to 12mmol/l. Three children had hypoglycaemia, and all of them were over five years old and all were without history of travel outside Lusaka City.

Table 3c: Pattern of Complicated Malaria – Hypoglycaemia

Variable	Hypoglycaemia	
	No	Yes
Sex		

male (%)	63(96.9)	2(3.1)
female (%)	43(97.7)	1(2.3)
Total (%)	106(97.2)	3(2.8)
Age		
<1 yr (%)	6(100)	0
1 – 5 yrs (%)	42(100)	0
>5yrs (%)	58(95.1)	3(2.8)
Travel		
no (%)	43(100)	0
yes (%)	63(95.5)	3(4.5)

4.4. OUTCOME OF MALARIA

Out of the 109 participants, 4 (3.67%) were treated as outpatients and 105 (96.33%) were admitted, with 101 (92.7%) subsequently discharged.

There were 4 (3.67%) deaths recorded, 2 (50%) males and 2 (50%) females. All the four deaths were due to cerebral malaria (CFR 21.1%) and occurred within 24 hours of admission. Two of the deaths occurred in children aged below 5 years, (aged two and four years, respectively), while the other two were among children over five years (aged six and fifteen years old, respectively). Two were from high density areas and the other two were from medium density areas. None of the four children who died had traveled outside town and none of them was HIV positive.

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CHAPTER 5

5. DISCUSSION

The study showed that despite Lusaka being in a very low transmission zone unlike most parts of the country, some aspects of the patterns of morbidity and mortality of malaria, such as seasonality of the disease, were similar across the country irrespective of the transmission intensity. For instance, the study was conducted during a ten month period and captured 62% of the total number of malaria cases seen during the entire study period. Majority of the participants were enrolled during the rainy season with a peak around February and March and there was a decline in incidence of malaria cases thereafter. This is comparable to earlier studies done elsewhere in the country including Macha, then an area of high transmission intensity (Biemba et la, 2000), and Nchelenge District which is an area of high transmission intensity (Nambozi et al, 2014 and Mukonka et al, 2014). In these studies the peak of malaria transmission also coincided with the peak of the rainy season, and was noted to decline after April with reducing rainfall.

On the other hand, the study also revealed some aspects about the pattern of malaria morbidity and mortality that are different from the rest of the country; for example, the prevalence of malaria in the study is 0.9%. In contrast, other hospital based studies have revealed higher prevalence. The Macha study referred to earlier showed a prevalence of 37.7% (Biemba et al, 2000), and in Nchelenge it ranged between 34 – 53% over a period of seven years (Mukonka et al, 2014). A tertiary hospital based Indian study revealed a prevalence of 6% during the study period (Jain et al, 2014). All these other studies were conducted in higher transmission settings and therefore the observation in this study is in keeping with what is expected in an area of very low transmission intensity such as is the current state of Lusaka City.

The study also revealed a prevalence of complicated malaria of approximately 50%. The only available comparable in-country study conducted among children is the hospital based Macha study in which the prevalence of complicated malaria was found to be 45.3% (Biemba et al, 2000). The difference noted is very small despite the two studies having been conducted in areas of very different transmission intensities. Elsewhere in Madrid, Spain, a hospital based study in a low transmission region revealed a prevalence of complicated malaria of 25% (Paredes et al, 2013).

The morbidity pattern of malaria in the study has shown a further shift in terms of age from the mean age of four years for the rest of the country (MOH, 2013) to affect more older children (age 5.6 years). This corresponds to results obtained in

other areas of low transmission settings in Tanzania and Ghana (Snow et al, 1997; Reyburn et al, 2005; Idro et al, 2006; Okiro et al, 2009).

The study has also demonstrated patterns that show a high rate of complicated malaria among infants, with notable reductions with increasing age. Similar findings were noted in an area of low transmission rate in Tanzania (Reyburn et al, 2005). According to Snow et al (1997) and Doolan et al (2009), such observations are attributable to lack of maternal NAI in areas of very low transmission rates as a result of lack or limited exposure to the malaria parasite and therefore rendering children, in the absence of this, and in addition to their generally immature immune system, highly susceptible to severe malaria.

The study also elucidated patterns suggestive of increasing proportions of cerebral malaria in relation to other forms of severe disease. The ratio of severe malarial anaemia to cerebral malaria is greatly reduced (1.68:1). This finding is in line with earlier studies in which similar trends have been noted in Tanzania and Kenya where cerebral malaria accounts for an increasingly large proportion of cases as one moves towards lower transmission rates (Snow and Marsh, 2002; Reyburn et al, 2005; Okiro et al, 2009; Carneiro et al, 2010). In the Macha study, severe anaemia was more than twice the number of cerebral malaria cases in keeping with trends usually reported in areas of high transmission intensity (Biemba et al, 2000).

The patterns of malaria morbidity and mortality in the study have also revealed an overall case fatality rate (CFR) for malaria of 3.7% which is higher than what has been reported in Nchelenge (0.1% - 0.3%) [Mukonka et al, 2014] and elucidates trends alluded to the differences in the transmission rates between the two settings. The high CFR can also be attributed to the fact that this is a referral hospital that generally receives referrals of severely ill children. However, this is in line with similar studies such as the Tanzanian study where the CFR for malaria in an area of low transmission intensity was higher (13%) compared to high and moderate transmission settings where the CFR was 7%, respectively (Reyburn et al, 2005).

The CFR for cerebral malaria in the study is comparable to that reported in the Macha study [Biemba et al, 2000]. Some studies have revealed a much higher CFR, for example, it was 37.8% in the Indian study while the CFR for the severe forms combined was 18.9% (Jain et al, 2014).

Finally, the mortality attributable to malaria has shown a pattern that is widely spread and affecting different age groups (from two years to 15 years). Existing evidence has shown that in areas of low transmission intensities, all age groups are susceptible to severe malaria, including death, whereas with increasing transmission intensities, older children and adults suffer less severe disease (Snow and Marsh, 2002).

CHAPTER 6

6. CONCLUSION

The scarcity of in-country studies focusing on morbidity and mortality patterns in various transmission zones make it difficult to draw conclusions from some of the noted study results.

The results however showed that the signs and symptoms of malaria already documented in literature are among the common manifestation of malaria even in the study population with fever being the commonest.

Severe malarial anaemia was the commonest pattern of morbidity of malaria, followed by cerebral malaria and hypoglycaemia secondary to malaria.

A younger age at presentation and a history of travel outside Lusaka were some of the noted risk factors for severe disease.

Cerebral malaria was a cause of mortality among children with malaria at UTH.

6.1. LIMITATIONS OF THE STUDY

- Not all parameters of severity of malaria could be demonstrated in the study due to lack of capacity by the laboratory to test all parameters (such as parasitaemia quantification and testing for lactate). At other times some results were not available for analysis (as is the case with some MPS results).

- The study was also unable to demonstrate the actual species of the actual plasmodium parasite involved.

- UTH is setup differently compared to other health institutions, making it difficult to generalize some aspects of the study.

6.2. RECOMMENDATIONS

- Severe anaemia malaria and cerebral malaria are the commonest forms of severe malaria seen at UTH and therefore need for availability of treatment guidelines as well as other management requirements at all times to avoid unnecessary deaths.

- There is need for similar studies in different transmission zones as well as at different levels of care to go hand in hand with the regular and robust surveys done at various levels country wide to show patterns over time.

CHAPTER 7

7. REFERENCES

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APPENDICES

7.1.1.Appendix i: INFORMATION SHEET

(A STUDY TO DETERMINE THE PATTERNS OF MORBIDITY AND MORTALITY OF MALARIA IN CHILDREN IN A VERY LOW TRANSMISSION SETTING)

1. **Why are we giving you this form?**

We are giving you this form, so as to give you information about the above named study which will be conducted at UTH and also to give you a chance to ask questions about this study. Then you can decide if you would like to take part in this study that is trying to find out how children found with malaria at UTH present as well as the things that may contribute to them getting infected with malaria.

2. **Who is carrying out this study?**

Dr. Patricia Mupeta Bobo is doing the study as part of specialist training at the University Of Zambia School Of Medicine.

3. **Background Information**

You are being invited to take part in the above mentioned study, were we would like to find out how children who are found with malaria at UTH present, as well as the things that may lead to them being infected with malaria. By participating in this study we will be able to get the information that may help us take care of them better by informing the relevant policy makers at the hospital to ensure that policies and interventions for this

problem of malaria are put in place. We believe this is very important information to all of us and you would help by   participating in this study.

You will be expected to take part in this study out of your own free-will and you child will still be attended to by the doctors even if you refuse to take part in the study. Should you agree and later change your mind you are free to withdraw your child from the study without suffering any penalties.

4. What Happens In This Research Study?

You will be interviewed now, and then your child will be further examined, and some blood and urine taken for tests. A total of 4 mL only of blood will be collected and sent to the laboratory to assess how the bone marrow, the kidney function, and the liver are working. The child will also be tested for HIV as well as to assess the amount of blood in the blood. 10 mL of urine will be collected and tested to assess the kidney function. The information collected will be kept confidential.

5. Possible Problems

We believe that the processes being used will not be harmful to you and the child participating in this study although needle prick will cause pain to your child while collecting blood samples. However if we notice anything peculiar to your child during or after information is collected, we will let you know and facilitate for him or her to receive appropriate intervention.

6. Benefits

It is hoped that the study will help produce information on the common presentation of malaria in children who are referred here for treatment and will result in appropriate measures being taken to control and treat the disease.

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7. Confidentiality

Your name and child's name will never be made public by the investigators. The medical record will be treated the same as all medical records at the health centers. A code number that makes it very difficult for anyone else to identify you will identify the research information gathered during this study from you. All information will be stored in a secure place. Information from this study will be used for research purposes and may be published; however, your name and your child's will not be made public by the investigators. It is possible that, after the study is over, we may want to look again at the laboratory and interview record data collected during this study to help us answer another question. If this happens, still your name will not be made public by the investigators. The Laboratory and interview data will be stored for five (5) years and there after the data will be shredded and burnt.

8. Research Related Injury

In the event that a problem results from a study-related procedure, Dr Patricia Mupeta Bobo in LUSAKA should be notified on + **260 955 154584** or contact the **ERES CONVERGE IRB** (see contact details section), and you or your child will be stabilized and facilitated to seek and receive appropriate medical care at the health facility.

9. Contact Details

Should you want further information about this study or your rights as a participant please use the details provided below.

Dr. Patricia Mupeta Bobo **Principle Investigator.** **University Teaching Hospital,** **Department of Paediatrics and Child Health.** **Cell phone Number: +260-955154584** **E-mail: mupetabobo@yahoo.com**	**The Secretary,** **ERES CONVERGE IRB,** **33 Joseph Mwilwa Road,** **Rhodes Park,** **LUSAKA**. **Cell phone numbers:** • **+260 966765 503** • **+260 955 155 634** **Email: eresconverge@yohoo.co.uk**

(A STUDY TO DETERMINE THE PATTERNS OF MORBIDITY OF MALARIA IN CHILDREN IN A VERY LOW TRANSMISSION SETTING)

Participant

I_____ (participant's parent or guardian's name, signature or thumb-print) have been informed about the study. I volunteer to have my child in the study. A copy of this form signed by me and one of the study investigators is being given to me.

Signature/Thumb_____

Signature of witness if thumb printed

_____

Date (D/M/Y) _____

Interviewer

I have explained this research study to the Participant. I am available to answer any questions now or in the future regarding the study and the Participant's rights.

Name of Investigator_____

Signature_____

Date (D/M/Y) _____

Apendix iii: ASSENT FORM

(A STUDY TO DETERMINE THE PATTERNS OF MORBIDITY OF

MALARIA IN CHILDREN IN A VERY LOW TRANSMISSION SETTING)

Participant

I_____ (participant's

name, signature or thumb-print) have been informed about the study. I volunteer to

be in the study. A copy of this form signed by me and one of the study investigators

is being given to me.

Signature/Thumb_____

Signature of witness if thumb printed

_____

Date (D/M/Y) _____

 Interviewer

I have explained this research study to the Participant. I am available to answer any

questions now or in the future regarding the study and the Participant's rights.

Name of Investigator_____

Signature_____

Date (D/M/Y) _____

A STUDY TO DETERMINE THE PATTERNS OF MORBIDITY OF MALARIA

IN CHILDREN IN A VERY LOW TRANSMISSION SETTING

---

a) Identification code: _____

b) Initials of participant: _____

c) Participant study number: _____

d) Date of the interview: _____

Part I: Demographics

a) Date of Birth: _____

b) Age: _____ Years: _____ Months: _____

c) Sex: 1. Male   2. Female

d) Area of Residence_____

e) For how long have you lived in Lusaka? _____

Part II: Presenting Complaints (tick whichever applies):

a) Fever   Y ☐   N ☐

b) Headache   Y ☐   N ☐

c) Vomiting   Y ☐   N ☐

d) Diarrhoea   Y ☐   N ☐

e) Cough   Y ☐   N ☐

f) Breathlessness   Y ☐   N ☐

g) Yellowing of eyes   Y ☐   N ☐

h) Loss of appetite   Y ☐   N ☐

i) Passing urine normally   Y ☐   N ☐

    a. If not, give details _____

j) Passing dark urine Y ☐   N ☐

k) Convulsions   Y ☐   N ☐

    a. If Yes, How many times? _____

l) Confusion/abnormal behaviour   Y ☐   N ☐

m) Other _____

Part III: Details of Presenting Complaints:

A. ITN ownership/Usage;

a) Do you have a mosquito net? 1. Yes ☐   2. No ☐

b) Does this child sleep under the mosquito net? 1. Yes ☐   2. No ☐

B. Recent History of Travel

a) History of travel by patient to a place outside Lusaka within the last 1 month?

    1. Yes ☐   2. No ☐

      i.   If Yes to _____

      ii. Date of travel_____

      iii. Date of return to Lusaka_____

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b) History of travel by member of household to a place outside Lusaka within the last

1 month?   1. Yes ☐   2. No ☐

c) History of receiving a visitor to the household from outside Lusaka within the last

1 month?   1. Yes ☐   2. No ☐

Part IV: Review of systems:

a) Cardio-Respiratory system:

1. Normal ☐   2. Abnormal ☐specify _____

b) Gastrointestinal system:

1. Normal ☐   2. Abnormal ☐specify _____

c) Genital-urinary system:

1. Normal ☐   2. Abnormal ☐specify _____

d) Neurology system:

1. Normal ☐   2. Abnormal ☐specify _____

e) Other systems

1. Normal ☐   2. Abnormal☐specify _____

Part V: Past medical history

a) **Any recent admissions (< 4 weeks):** 1. Yes ☐   2. No ☐

b) **Do you suffer/have suffered from any serious illness such as:**

1. SCD ☐   2. D.M.☐   3. TB ☐

4. Others _____

c) **HIV Status:**

1. Positive ☐   2. Negative ☐ 3. Test not done ☐

Part VI: Drug history

a) Anti malarial drug history

1.   Did this child receive any anti-malaria in the last 4 weeks? i. Yes ☐ ii. No ☐

2.   If yes, which anti-malarial drug? i. Fansidar ☐   ii. Co-artem ☐ iii. Quinine ☐

b) Other drugs:

_____

Part VII: PHYSICAL EXAMINATION

a) General appearance: 1. Well   ☐ 2. Ill   ☐

b) Vitals

1. Pulse:_____

2. Respiratory rate:_____

3. Temp:_____

4. BP:_____

5. Glasgow Coma scale_____

c) Anthropometry

1. Height/length _____ cm.

2. Weight_____ Kg.

3. MUAC _____mm

4. Weight for height Z-Score 1. < -3 ☐   2.<-2 ☐   3.<-1☐   4. Median ☐

1. Bilateral pedal oedema i. Yes ☐   2.No ☐

d) General examination

1. Pallor: 1. Present ☐   2. Absent   ☐

2. Jaundice   1. Present ☐   2. Absent   ☐

3. Cyanosis   1. Present ☐   2. Absent   ☐ .

e) systems/organs

SYSTEM/ORGAN	NORMAL	ABNORMAL	SPECIFY FINDINGS (IF ABNORMAL)
skin			
Eyes			
Ears, Nose			
Oral			
Lymph nodes			
Heart			
Lungs			
Abdomen			
Urogenital			
Musculoskeletal			
Neurological			

Part VIII: Investigations

a) Rapid malaria test (RDT):   1. Positive ☐   2. Negative ☐

b) Malaria Blood slide (MPs): 1. Positive ☐   2. Negative ☐

c) Urinalysis:

    1. Urine colour: Normal _____abnormal _____

    2. Blood_____, Glucose_____, Protein_____, Leucocytes_____,

        Urobilinogen_____, Ketones _____

d) RVD sero-status 1. Positive ☐   2. Negative ☐

e) Random Blood Sugar_____mmol/l

f) FBC: WBC ____, Hb ____, Platelet_____, Neutrophil_____

g) RFT: Creatinine_____ Urea_____

Part IX: Type of Malaria

    1. Uncomplicated ☐

    2. Complicated:

        a. Cerebral malaria   ☐

        b. Pulmonary edema ☐

        c. Circulatory collapse/shock ☐

        d. Acute renal failure ☐

        e. Severe anemia, and/or bleeding ☐

        f. Metabolic Acidosis ☐

        g. Hypoglycemia ☐

        h. Clinical jaundice plus evidence of other vital organ dysfunction ☐

        i.   Haemoglobinuria ☐

        j.   Hyperparasitaemia ☐

        k. Hyperlactataemia. ☐

Part X: Treatment

1. Coartem ☐

2. Quinine ☐

3. With other ☐ _____

_____

Special interventions

_____

_____

Part XI: Outcome of Hospital visit

1. Treated as an Out-patient ☐

2. Died in Ao1 ☐

3. Admitted ☐

4. Died within 24 hours of presentation to UTH ☐

5. Discharged ☐ Date_____

6. Died ☐ Date_____

7. LAMA* ☐ Date_____

8. Absconded ☐ Date_____

Signature: _____ Date _____

Data entry date _____

* LAMA – Left against medical advice

1st September, 2014

Ref. No. 2014-June-012

The Principal Investigator
Dr. Patricia Mupeta Bobo
The University of Zambia
School of Medicine
Dept. of Paediatrics and Child Health
Private Bag RW 1X,
LUSAKA.

Dear Dr. Bobo,

**RE: A STUDY TO DETERMINE THE PATTERNS OF MORBIDITY OF
MALARIA IN CHILDREN IN A VERY LOW TRANSMITTING
SETTING.**

Reference is made to your corrections dated 22nd August, 2014. The IRB resolved to approve this study and your participation as principal investigator for a period of one year.

Review Type	Ordinary	Approval No. 2014-June-012
Approval and Expiry Date	Approval Date: 1st September, 2014	Expiry Date: 31st August, 2015
Protocol Version and Date	Version-Nil	31st August, 2015
Information Sheet, Consent Forms and Dates	• English, Bemba, Nyanja.	31st August, 2015
Consent form ID and Date	Version-Nil	31st August, 2015
Recruitment Materials	Nil	31st August, 2015
Other Study Documents	Data Collection Sheet	31st August, 2015
Number of participants approved for study	107	31st August, 2015

Specific conditions will apply to this approval. As Principal Investigator it is your responsibility to ensure that the contents of this letter are adhered to. If these are not adhered to, the approval may be suspended. Should the study be suspended, study sponsors and other regulatory authorities will be informed.
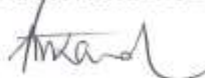
Conditions of Approval

- No participant may be involved in any study procedure prior to the study approval or after the expiration date.
- All unanticipated or Serious Adverse Events (SAEs) must be reported to the IRB within 5 days.
- All protocol modifications must be IRB approved prior to implementation unless they are intended to reduce risk (but must still be reported for approval). Modifications will include any change of investigator/s or site address.
- All protocol deviations must be reported to the IRB within 5 working days.
- All recruitment materials must be approved by the IRB prior to being used.
- Principal investigators are responsible for initiating Continuing Review proceedings. Documents must be received by the IRB at least 30 days before the expiry date. This is for the purpose of facilitating the review process. Any documents received less than 30 days before expiry will be labelled "late submissions" and will incur a penalty.
- Every 6 (six) months a progress report form supplied by ERES IRB must be filled in and submitted to us.
- ERES Converge IRB does not "stamp" approval letters, consent forms or study documents unless requested for in writing. This is because the approval letter clearly indicates the documents approved by the IRB as well as other elements and conditions of approval.

Should you have any questions regarding anything indicated in this letter, please do not hesitate to get in touch with us at the above indicated address.

On behalf of ERES Converge IRB, we would like to wish you all the success as you carry out your study.

Yours faithfully,
ERES CONVERGE IRB

Dr. E. Munalula-Nkandu
BSc (Hons), MSc, MA Bioethics, PgD R/Ethics, PhD
CHAIRPERSON

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