PREVALENCE OF PLASMODIUM FALCIPARUM INFECTION IN FEBRILE CHILDREN PRESENTING AT THE UNIVERSITY TEACHING HOSPITAL; CLINICAL PRESENTATION AND OUTCOME

BY:

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A dissertation submitted to the University of Zambia in partial fulfilment of the requirements of the degree of Master of Medicine in Paediatrics

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DECLARATION

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

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This dissertation of Mwangelwa Mubiana is approved as partial fulfilment of the requirements for the award of the Master of Medicine in Paediatrics by the University of Zambia.

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ACRONYMS

ADD : Acute diarrhoeal disease

C. Malaria: Cerebral malaria

FTT : Failure to thrive

HCT : Haematocrit

PEM : Protein - energy malnutrition

PTB : Pulmonary tuberculosis

RBC : Red blood cell

RTI : Respiratory tract infection

S. Anaemia : Severe anaemia

SCD : Sickle cell disease

S. Malaria : Severe malaria

TSS : Tropical splenomegaly syndrome

URTI : Upper respiratory tract infection

UTH : University Teaching Hospital

WHO : World Health Organisation

ABSTRACT

Fever, which is a feature of many childhood illnesses, is the commonest presentation of falciparum malaria, a common and potentially serious disease.

To determine the prevalence of *Plasmodium falciparum* infection in febrile children, it's clinical presentation and outcome, a study was conducted at the University Teaching Hospital between January and April 1999. Four hundred and ninety-seven febrile children between 6 months and five years of age were screened by peripheral blood examination for asexual *P. falciparum* parasitaemia.

The prevalence of *Plasmodium falciparum* parasitaemia in febrile children was found to be 29.4 percent. The first recorded clinical diagnosis of these patients who had malaria parasitaemia on admission was malaria in 60.7 percent of the patients followed by respiratory tract infection (10.3 percent). The commonest clinical features in decreasing frequency were anorexia, vomiting, cough, convulsions and splenomegaly. Anaemia, which was defined as a haematocrit of less than 33 percent, was a feature in 85.1 percent of the patients. The parasite densities ranged between 0.2 and 53.3 percent (mean 5.33 percent). High parasite density was associated with a clinical diagnosis of malaria on admission (p-value 0.050, odds ratio 2.114).There was, however, no significant association between parasite density and convulsions or parasite density and impaired consciousness. Almost all the patients received anti-malarial treatment. In addition

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Fever, which is a feature of many childhood illnesses, is the commonest presentation of falciparum malaria, a common and potentially serious disease.

To determine the prevalence of *Plasmodium falciparum* infection in febrile children, it's clinical presentation and outcome, a study was conducted at the University Teaching Hospital between January and April 1999. Four hundred and ninety-seven febrile children between 6 months and five years of age were screened by peripheral blood examination for asexual *P. falciparum* parasitaemia.

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54 (37.2 percent) of the patients also received an antibiotic, of which penicillin was the commonest (70.4 percent). Seventeen patients (11.7 percent) received blood transfusions. After three days of follow up 97 (66.9 percent) of the patients were discharged and ten (6.9 percent) died. No association was observed between parasite density and outcome.

This study showed that the majority of the children between six months and five years of age presenting with fever at the UTH do not have demonstrable *Plasmodium falciparum* parasitaemia on admission. The overall outcome of the patients was good. The mortality was 6.9 percent by the third day of admission and it was associated with severe disease as evidenced by the admitting doctors' diagnoses.

CHAPTER ONE

1.0 INTRODUCTION

Malaria is a serious problem world wide with an estimated 100 countries and territories being at risk (WHO, 1997). The global estimate of clinical cases stand at 300-500 million annually. The World Health Organisation estimates that 1.5 –2.7 million people die from malaria each year and approximately one million deaths among children under five years of age are attributable to malaria alone or in combination with other diseases (1).

In Africa, the importance of malaria has long been recognised. Countries in tropical Africa account for more than 90 percent of the total malaria incidence and the great majority of malaria deaths (1). Between one and two million African children die from malaria each year. This means that in Africa one child dies from malaria every fifteen seconds (2).

The malaria vector breeds in a warm wet climate. The African region's humidity and vegetation favours the vector's propagation so well that it has been impossible to eradicate the disease using the approaches which have worked in the Mediterranean countries and some of the fringe areas of Africa. The realisation of the almost unachievable goal to eradicate malaria led to the adoption of a more achievable goal to control the disease. This led to the birth of 'roll back malaria' which is a programme aimed at control rather than eradication of the disease.

Zambia is a landlocked country in sub-Sahara Africa with an estimated population of 10 million, 16 percent of it being less than 5 years old (5). It experiences a tropical climate and has three recognizable seasons. It is cold and dry from May to August, hot and dry from September to October and warm and wet from November to April. Prevalence of clinical malaria tends to be highest in the warm wet season due to availability of breeding grounds for the vector the *anopheles* mosquito. This seasonal trend has also been demonstrated in Malawi (a neighbouring country) but only in early infancy where it was found that *Plasmodium falciparum* parasitaemia prevalences were markedly lower in the dry season than during the rainy or post- rainy season. However, by ten months of age the prevalence was uniformly high (60-80 percent) regardless of season (9).

From 1978 to 1995, the malaria incidence in Zambia has steadily increased from 138/1000 to 288/1000, the most affected age group being 1 to 5 years with equal male to female ratios (5). Mortality due to malaria averages 14.8 percent in hospitals and 21.1 percent in health centres (5).

The University Teaching Hospital in Lusaka is a tertiary hospital which caters for referred patients from within Lusaka and the rest of the country. The paediatrics department of the hospital has a laboratory which is able to test for malaria parasites within a reasonable period of time. Outpatients actually wait for the results. However, this laboratory only operates during normal working hours, i.e. from 08:00 hours to 16:00 hours during weekdays and mornings only on Saturdays. Thus patients seen outside laboratory working hours may not have the opportunity for rapid laboratory diagnosis. Furthermore, high patient load and limited resources may not allow for every patient suspected to have malaria to be tested for malaria parasites. Thus many

patients are diagnosed as having malaria based purely on clinical suspicion.

In 1997, clinical malaria accounted for 3,762 admissions (19.5 percent of the total number of admissions) in the department of paediatrics. The month of highest prevalence was April (end of rainy season) which accounted for 13.9 percent of the total malaria cases for the year. Lowest prevalence was in August (end of cold dry season) which had 5.5 percent of the total malaria cases. The number of deaths due to malaria was 254 (7.6 percent of the total number of deaths) i.e. a case fatality rate of 67.5 per 1000. The most affected age group was 1-4 years with 1,765 cases (46.9 percent) followed by the under 1 year old accounting for 1,147 cases (30.5 percent). Overall in 1997, malaria was the number 3 cause of mortality after malnutrition and pneumonia. However it was the number 1 cause of admissions followed by pneumonia (UTH records – unpublished).

The clinical presentation of malaria is very non-specific, making the diagnosis very difficult. In a malaria endemic area, detection of asexual parasitaemia does not signify clinical malaria as asymptomatic parasitaemia prevalence is high (6,28). Fever has been reported as the main symptom of malaria (8). Many other childhood illnesses however, present with fever.

Despite no studies having been done in our environment to determine the relationship between fever and *Plasmodium falciparum* infection in children, the usual practice by clinicians is to include antimalarial treatment in most febrile children.

CHAPTER TWO

2.0 STUDY JUSTIFICATION

Many childhood illnesses are associated with fever as a major component. Usually the development of fever is one of the major reasons for the health-seeking behaviour of the care givers. In an environment where malaria is a major cause of morbidity and mortality in childhood, it is of interest to know what proportion of these febrile episodes might be due to malaria in a tertiary centre.

2.1 CURRENT SITUATION

The current trend in our environment at the first level of health care is to include an anti-malarial for every febrile episode irrespective of the presence or absence of any obvious cause of the fever. This is a recommendation of the Integrated Management of Childhood Illnesses. Patients presenting to a tertiary hospital will usually have been attended to by other health care providers and only those who seem to have serious illnesses or have not responded to initial treatment will end up being referred. Nevertheless, there is a proportion of patients who present to UTH without having passed through a primary health care centre.

CHAPTER THREE

3.0 LITERATURE REVIEW

Malaria is the clinical condition caused by infection with the parasite plasmodium. There are four recognised species causing human disease, namely *P. falciparum, P. vivax, P. malariae* and *P. ovale.* Most malaria cases in Africa are due to *P. falciparum* with less than 5 percent due to other species (2). This species causes the most malignant form of the disease with a high risk of mortality and morbidity if not treated early.

Malaria continues to be a major health problem with over 40 percent of the world's population being at risk (19). It affects mostly the tropical and subtropical regions of the world. The malaria incidence in Africa has been reported to be increasing with incidence growth rates of 7.3 percent for Zambia, 10.4 percent for Togo and 21.0 percent for Rwanda. Between 1975 and 1990 mortality due to malaria was reported to be rising (27).

Endemicity of malaria may be classified as stable or unstable. Stable malaria refers to intense transmission through out the year and unstable malaria refers to seasonal transmission with wide yearly variations (24).

Endemicity of malaria is estimated by the spleen rate and parasite rate. The spleen rate is defined as the proportion of children aged 2 to 9 years with splenomegaly and the parasite rate is the proportion of persons in a defined age group or on a given date with microscopically proven parasitaemia (20).

Hypoendemicity refers to a spleen rate or parasite rate of 0-10 percent in children 2-9 years old. Mesoendemicity is a spleen rate or parasite rate of 11-50 percent in children 2-9 years old. Hyperendemicity is a spleen rate or parasite rate consistently greater than 50 percent in children 2-9 years old, with the adult spleen rate also being high. In holoendemicity, the spleen rate or parasite rate is greater than 75 percent in children 2-9 years old, the adult spleen rate is low and the parasite rate in infants is high (20).

In Zambia malaria is endemic in the whole country with endemicity ranging from holo/hyper along the major river valleys to meso and hypoendemism in urban centres. It differentially affects all age groups with young children, pregnant women and non-immunes bearing the brunt of the disease . Crude parasite rates for the country (general population) range from 75-90 percent in rural areas to 20-55 percent in urban areas (4).

In Samfya district (a rural setting), Mwanakasale and Hautvasi found the prevalence of malaria parasitaemia in children aged between 4 months and 19 months to be 81.9 percent. The prevalence of malaria in children less than one year was 76.1 percent, *P. falciparum* only accounting for 60.1 percent and mixed plasmodium infections 12.4 percent. In those one year and above, the prevalence was 88.7 percent with *P. falciparum* only 60.8 percent and mixed infections 22.7 percent. They found a statistically higher prevalence of mixed infections in children one year and above than in children less than one year old (6).

Falciparum malaria has an incubation period of 8-15 days. The child then develops non-specific symptoms such as lethargy or irritability, headache, fever, anorexia, nausea and vomiting (17,18, 20). Complicated malaria may present as severe anaemia, cerebral malaria, generalised

convulsions, renal failure, hypoglycaemia, pulmonary oedema, hypotension (algid malaria), spontaneous bleeding, haemoglobinuria. hyperpyrexia (temperature ≥ 42°C) or hyperparasitaemia (>5%) (19).

Although fever is a constitutional symptom of many other illnesses, it was reported to be the main symptom in more than 95 percent of malaria episodes in children aged 0-9 years in Tanzania (8). In a study done by Svenson and others to determine if clinical presentation could be used to predict malaria infection in febrile patients with recent travel to a malaria-endemic area there were no reported symptoms that were very helpful in predicting malaria infection. It was found that though the presence of tertian fever was predictive of having malaria, it was present in so few patients that the sensitivity was only 40 percent while the specificity was 95 percent (7).

In Papua New Guinea, Genton and others found that the prevalence of fever with parasitaemia was highest in the one to four year old children (4 percent), accounting for 74 percent of all fevers in this age group but only 28 percent of those in infants and 42 percent of those in adults aged more than 20 years. Parasitaemia with asexual stages of *Plasmodium falciparum* was significantly more present in fever cases than in healthy (asymptomatic) individuals in the 1-4 year old age group. This age group also had the highest proportion of high density *P. falciparum* fevers. They also found the prevalence of fever with malaria parasitaemia to be highest at the start of the wet season (3).

In rural Malawi, fever history in the previous two weeks was significantly associated with parasitaemia, sensitivity ranging from 50 to 65 percent. Increasing age was significantly

associated with increasing parasite density in the first year of life. Specificity of a recent fever history as a predictor of smear positivity decreased as a function of age from more than 70 percent in the first three months of life to 41-47 percent over the last four months of infancy (9).

A study done in Tanzania to determine whether fever was a good sign for clinical malaria found that in infants, fever was not a good predictor of malaria and only in the 1-4 year old age group was fever most indicative of clinical malaria. In children 5-9 years of age, there was less increase in temperature associated with malaria (10).

A study done in Nigeria in children aged 6-60 months showed no association between malaria and diarrhoea as is widely believed (11).

The diagnosis of malaria thus depends on the clinicians clinical evaluation and the laboratory demonstration of asexual parasitaemia. However in an area with perennial malaria transmission, asexual parasitaemia may persist through out the year making the diagnosis even more difficult as the malaria symptomatology may mimic many other illnesses. Some researchers have thus tried to define cut off points for parasite densities which are more likely to be associated with clinical illness (3,8,10,28).

Besides demonstration of asexual parasites on a blood film, antigen tests have been developed to detect *Plasmodium falciparum* (12,13). . Parasite F test assays histidine-rich protein 2 (HRP-2) antigen and has a sensitivity of 96.5-100 percent with asexual parasitaemia of greater than 60 parasites/μL (12). Histidine-rich protein 2 (HRP-2) is a water-soluble antigen released by blood stages of *P.falciparum.* It circulates in blood after elimination of viable *P.falciparum.* It

is not detectable in blood six days after starting curative chemotherapy (12). These antigen tests are currently expensive and are not readily available in most clinical settings. However, they would be useful in a setting without readily available laboratory services. Other diagnostic test include direct observation of centrifuged blood (22) and measurement of lactate dehydrogenase activity of *Plasmodium falciparum* (23).

Chloroquine has remained the first line drug in the treatment of uncomplicated malaria in Zambia. Second line drugs include sulfadoxine/pyrimethamine, halofantrine and quinine. For the treatment of severe and complicated malaria, quinine is the drug of choice.

Resistance to chloroquine is defined as follows:

RI – asexual parasites disappear by day 6 and reappear by day 28 of treatment

RII – asexual parasitaemia is reduced to 25 percent or less of the original level during the first 48 hours of treatment but no clearance.

RIII – asexual parasitaemia is reduced by less than 75 percent during the first 48 hours of treatment or it continues to rise (24).

Varying degrees of resistance to chloroquine have been demonstrated in different parts of Africa (15, 16).

In Zambia, a study done in several parts of the country in febrile children aged five years and below identified RIII or RII resistance in 34 percent to 70 percent of the children. Clinical failure was identified in 31 to 54 percent of the cases, of whom 25 to 66 percent failed by day three, 4 to 13 percent between days four and seven and 27 to 66 percent after day seven of treatment (25).

Another study in urban Lusaka also demonstrated high levels of resistance to chloroquine. In this study, which was done in a low transmission season, 542 clinically suspected malaria cases were screened. Those with positive blood slides were 117 (21.5 percent). Resistance to chloroquine was demonstrated in 40 percent of the cases and it was found to be inversely related to age (26). This rising chloroquine resistance will further worsen the malaria situation as chloroquine is used in many homes at the onset of any fever.

CHAPTER FOUR

4.0 OBJECTIVES

4.1 General Objective

To determine the prevalence of *P. falciparum* malaria in febrile children presenting to the UTH Department of Paediatrics and Child Health, it's clinical features and outcome.

4.2 Specific Objectives

1. To determine the prevalence of *Plasmodium falciparum* asexual parasitaemia in febrile children (axillary temperature ≥37.5°C).
2. To determine what proportion of children with fever and asexual *P. falciparum* parasitaemia are diagnosed as having malaria on clinical grounds by the admitting doctor.
3. To determine the associated clinical features.
4. To determine the parasite density and it's association with clinical presentation.
5. To evaluate the outcome in relation to parasite density and treatment.

CHAPTER FIVE

5.0 METHODOLOGY

5.1 Study Design

This was a prospective descriptive study of children admitted with fever at the University Teaching Hospital's Department of Paediatrics and Child Health.

5.2 Study Population

5.2.1 Site Description

The study was carried out in the Department of Paediatrics and Child Health of the University Teaching Hospital of Zambia. The UTH is a referral hospital which attends to both referred patients from all levels of health care and self referrals. Febrile children were recruited from the paediatrics admission ward. The admission ward is a short stay ward where children are admitted before being transferred to the main wards or discharged home if they recover early.

The Department of Paediatrics and Child Health has a laboratory which is able to carry out light microscopic examination within a reasonable period of time. This laboratory functions from 08:00 hrs to16:00 hrs during normal working days (Monday to Friday) and from 08:00 hrs to 12:00 hrs on Saturdays. It does not function on public holidays and Sundays.

5.2.2 Subject Selection

Selection criteria:

1. axillary temperature on admission of $\geq 37.5°C$
2. age above six months and below five year

Exclusion criteria:

1. history of taking an antimalarial in previous one week except those with history of taking a stat dose of an antimalarial on referral
2. non-consenting

5.3 Sampling Frame

This study was conducted from January to April 1999 which constitutes the warm wet season. Sampling was done from Mondays to Fridays. Weekdays were chosen due to the guaranteed availability of laboratory services.

The first ten patients fulfilling the criteria were recruited each day.

The estimated sample size was 130 based on the assumption that the prevalence of *P. falciparum* asexual parasitaemia in febrile children is 20 to 30 percent. At least 390 febrile children needed to be screened to obtain this sample size.

5.4 Subject Management

A questionnaire was administered to every attending adult/care-giver. It was filled in by the researcher/research assistant upon interviewing the care-giver. The attending physician's admission diagnoses (first two if more than two) were recorded.

5.4.1 Investigations

After cleaning the tip of the thumb with a spirit swab, a prick was made using a blood lancet. A drop of blood was placed on two glass slides. Blood from the same site was collected in a glass tube (capillary tube).

The smears were stained by 10% Giemsa and examined by an experienced laboratory technician.

Identification of asexual forms of *Plasmodium falciparum* on the thick blood films were considered as positive for *P. falciparum* malaria. A maximum of 100 fields were looked at using oil immersion at ×100 objective.

To determine the parasite density the thin slides were examined only if the thick slide was positive. A total of at least 500 RBCs were counted (both parasitised and unparasitised) using oil immersion at ×100 objective. Parasite density was calculated as a percentage using RBCs as the denominator as follows:

$$\frac{\text{number of parasitised RBCs}}{\text{number of unparasitised + parasitised RBCs}} \times 100$$

The capillary tubes were spun in a centrifuge at 3000 rotations per minute for five minutes and the haematocrit determined.

5.4.2 Clinical Evaluation

A general examination of the patients was done and splenomegaly was specifically looked for. The patients were then followed up for a maximum of three days or until discharge or death, whichever was earlier.

Treatment given was recorded.

5.4.3 Outcome Measures

The outcome measures after three days of follow up were:

1. Resolution of fever
2. General condition remained unchanged or worsened
3. Discharge
4. Death

5.5 Data Management

The prevalence of *Plasmodium falciparum* parasitaemia in febrile children was determined manually.

The rest of the data was analysed by Epi Info statistical soft ware. Frequency and cross tabulation tables were used to describe the variables and to determine any relationships.

5.6 Ethical Issues

This study was carefully explained to every accompanying responsible adult of every patient. Both written and verbal consent were obtained from the same. The research proposal was approved by the research ethics committee of the University of Zambia.

CHAPTER SIX

6.0 RESULTS

6.1 Prevalence of falciparum malaria

A total of 497 febrile children were screened. Out of these 146 had positive blood slides but one was lost to follow up. This gives a prevalence of 29.4%.

145 patients were followed up, which was fifteen more than the estimated sample size.

6.2 Fever Characteristics

The duration of fever ranged from 1 to 60 days with a mean of 5.4 days.

In 60 patients (41.4%) fever was said to have been constant and in 85 (58.6%) it was not constant.

6.3 Travel out of Lusaka

Fourty six patients (31.7%) had been out of Lusaka in the previous fourteen days and 99 (68.3%) had not.

6.4 Associated clinical features

Table 1

Feature	Frequency	Percent
Anorexia	88	60.7
Vomiting	60	41.4
Cough	40	27.6
Fits	40	27.6
Splenomegaly	32	22.1
Impaired consciousness	24	16.6
Diarrhoea	20	13.8
Difficulty in breathing	19	13.1

Anorexia and vomiting were the commonest clinical features found. Other features which were common were cough, fits and splenomegaly.

6.5 Anaemia

This was determined by measuring haematocrits. All those with haematocrits less than 33 percent (haemoglobin 11g/dl) were considered anaemic. A total of 134 patients had their haematocrits determined. Those without haematocrits had either the capillary tubes broken or the blood leaked out. Anaemia was detected in 85.1 percent of the patients. Severe anaemia, defined as haematocrit less than 15 percent, was found in 12.7 percent.

Table 2 Anaemia

Anaemic: haematocrit < 33 percent; Not anaemic : haematocrit ≥ 33 percent

	Frequency	Percent
Anaemic	114	85.1
Not anaemic	20	14.9
TOTAL	134	100.0

6.6 Clinical diagnosis on admission

Both the first and the second diagnoses were recorded.

Table 3 First diagnosis

Diagnosis 1	Frequency	Percent
Malaria	88	60.7
RTI / Pneumonia	15	10.3
Anaemia	13	9.0
Febrile illness	6	4.1
Meningitis	6	4.1
URTI	4	2.8
Febrile fits	3	2.1
ADD	2	1.4
Kwashiorkor	2	1.4
TSS	2	1.4
Acute nephritis	1	0.7
Dysentry	1	0.7
FTT	1	0.7
PTB	1	0.7

Of all the patients who had malaria as a first diagnosis (60.7percent), 42 (29.0percent) were said to have had severe malaria of whom 10 (6.9 percent) had cerebral malaria. One patient (0.7 percent) was thought to have had chronic malaria.

Table 4 Second diagnosis

Diagnosis 2	Frequency	Percent
Malaria	37	46.3
Anaemia	30	37.6
Pneumonia	4	5.0
Hypoglycaemia	2	2.5
Febrile illness	1	1.3
PEM	1	1.3
Meningitis	1	1.3
SCD	1	1.3
Septicaemia	1	1.3
URTI	1	1.3
Viral infection	1	1.3

Of those who did not have malaria as a first diagnosis, it appeared as a second diagnosis in 46.3 percent. This accounted for 24.1 percent of the total number of cases.Two patients were diagnosed as having severe malaria. Sixty five cases did not have a second diagnosis.

6.7 Parasite densities

A total of 132 patients had their parasite densities determined. The shortfall is due to spoiled slides. The densities ranged from a minimum of 0.2 percent to a maximum of 53.3 percent, with a mean of 5.33 percent.

The parasite densities were grouped as follows: Low: parasite density ≤5 percent;

High: parasite density > 5 percent

Table 5 Parasite density

Parasite density	Frequency	Percent
Low	82	62.1
High	50	37.9
TOTAL	132	100.0

6.7.1 Relationship between parasite density and anaemia

Table 6

	Parasite density		TOTAL
	High	Low	
Anaemic	44	61	105
Not anaemic	4	14	18
TOTAL	48	75	123

P- value = 0.114; Odds ratio = 2.525; 95% confidence interval = 0.812 to 7.774

Although there was a two times likelihood of patients with high parasite densities (>5 percent) to be anaemic (odds ratio =2.525), the association between parasite density and anaemia was not

significant (p- value =0.114).

6.7.2 Relationship between parasite density and diagnosis

Table 7a Diagnosis 1

	Parasite density		
DIAGNOSIS 1	High	Low	TOTAL
Malaria	18	26	44
S. Malaria	18	19	37
Anaemia	4	7	11
Pneumonia / RTI	2	12	14
Meningitis	2	4	6
Febrile illness	1	5	6
URTI	2	2	4
TSS	1	1	2
Febrile fits	1	5	6
Acute nephritis	0	1	1
ADD	0	1	1
Dysentry	1	0	1
FTT	1	0	1
Kwashiorkor	0	1	1
PTB	0	1	1
TOTAL	50	82	132

Table 7b Relationship between clinical diagnosis of malaria and parasite density

DIAGNOSIS 1	Parasite density		TOTAL
	High	Low	
Malaria	36	45	81
Other	14	37	51
TOTAL	50	82	132

p- value = 0.050; odds ratio = 2.114; 95% confidence interval = 1.000 to 4.463

Of the 81 patients with a clinical diagnosis of malaria and had their parasite densities determined, 36 (44 percent) had parasite densities > 5 percent and 45 (66 percent) had densities ≤ 5 percent. Sixty percent of the patients with cerebral malaria had parasite densities > 5 percent. Of the 51 patients with a first diagnosis other than malaria and had parasite densities determined, 14 (27.5 percent) had parasite densities > 5 percent and 37 (72.5 percent) had densities ≤ 5 percent.The patients with high parasite densities were two times more likely to have a clinical diagnosis of malaria than those with lower parasite densities (odds ratio 2.114, p- value 0.050).

Table 8a Diagnosis 2

DIAGNOSIS 2	Parasite density		TOTAL
	High	Low	
Malaria	9	25	34
Anaemia	11	5	26
Pneumonia	2	1	3
Hypoglycaemia	0	2	2
Febrile illness	1	0	1
Meningitis	1	0	1
PEM	0	1	1
SCD	0	1	1
Septicaemia	0	1	1
URTI	1	0	1
Viral infection	0	1	1
TOTAL	25	47	72

Only one patient with a second diagnosis of malaria was said to have had severe malaria. The patient had a low parasite density. Of the patients with a second diagnosis of anaemia, six were diagnosed as having severe anaemia. Three of these had a low parasite density and the other three had a high parasite density.

Table 8b Relationship between clinical diagnosis of malaria and parasite density

DIAGNOSIS 2	Parasite density		TOTAL
	High	Low	
Malaria	9	25	34
Other	16	22	38
TOTAL	25	47	72

p- value = 0.164; odds ratio = 0.495; 95% confidence interval = 0.185 to 1.325

Of those with malaria as a second diagnosis and had their parasite densities determined (34), 26.4 percent had parasite densities greater than 5 percent. This percentage is much lower than that of those with malaria as a first diagnosis. The likelihood of patients with a higher parasite density being diagnosed as malaria was not more than that of those with a low density. However, patients with a second diagnosis other than malaria may already have malaria as a first diagnosis.

6.7.3 Relationship between parasite density and convulsions

Table 9

	Parasite density		
	High	Low	TOTAL
Fits	12	21	33
No fits	38	61	99
TOTAL	50	82	132

P -value = 0.835; Odds ratio = 0.917; 95% confidence interval = 0.410 to2.056

There was no significant association between the presence or absence of convulsions and parasite density.

6.7.4 Relationship between parasite density and impaired consciousness

Table 10

	Parasite density		
	High	Low	TOTAL
Impaired	7	12	19
Not impaired	43	70	113
TOTAL	50	82	132

P -value = 0.919; Odds ratio = 0.950; 95% confidence interval = 0.357 to 2.535

There was no significant association between level of consciousness and parasite density.

6.7.5 Relationship between parasite density and outcome.

Table 11

OUTCOME	Parasite density		TOTAL
	High	Low	
Fever resolution	16	16	32
Unchanged or worse	0	2	2
Discharge	32	60	92
Death	2	4	6
TOTAL	50	82	132

Of the patients whose fever resolved, there was an equal distribution between the two parasite density groups. Two patients with parasite densities equal to or less than 5 percent and none with densities greater than 5 percent remained in the same condition or worsened.

About two thirds of the patients who were discharged had parasite densities equal to or less than 5 percent and a third had parasite densities greater than 5 percent. The same ratio applies to the patients who died but the numbers in this group are much smaller.

6.8 Treatment

Three groups of treatment were looked at: antimalarial, antibiotic and blood transfusion.

Table 12

Treatment	Frequency	Percent
Antimalarial	142	97.9
Antibiotic	54	37.2
Blood transfusion	17	11.7

Type of antibiotic:

a) septrin or erythromycin – 15 (27.8%)

b) penicillins –38 (70.4%)

c) other –1 (1.8%)

Almost all the patients received anti-malarial treatment.

A large fraction of patients also received antibiotics (37.2 percent), with penicillins accounting for 70.4 percent of the antibiotics.

Blood transfusions were given in 11.7 percent of the patients.

6.9 Outcome after three days of follow up

Outcome measures were:

1 -resolution of fever

2 -condition unchanged or worsened

3 -discharge from hospital

4 -death

Table 13 Outcome

Outcome	Frequency	Percent
Fever resolved	35	24.1
Unchanged or worse	3	2.1
Discharge	97	66.9
Death	10	6.9
TOTAL	145	100

After three days of treatment the majority of the patients (66.9 percent) were discharged from hospitaland 6.9 percent had died. Of those who were discharged, thirteen (13.4 percent) still had fever (temperatures ranging from 37.5°C to 38°C).

Table 14 Mortality

Diagnosis	Treatment	Haematocrit	Parasite density	Blood transfusion
1. Meningitis 2. Malaria	1. Antibiotic 2. Quinine	18	2.6	No
1. S. Malaria 2. S. Anaemia	1. Quinine	15	-	Yes
1. S. Malaria 2. Anaemia	1. Quinine 2. Antibiotic	-	-	No
1. C. Malaria 2. Meningitis	1. Quinine 2. Antibiotic	33	19.3	No
1. S. Malaria 2. Anaemia	1. Quinine	24	2.5	Yes
1. S. Anaemia 2. -	1. Quinine	26	3.4	Yes
1. RTI 2. Malaria	1. Quinine	24	6.8	No
1. S. Malaria 2. S. Anaemia	1. Quinine	14	3.5	No
1. S. Anaemia 2. S. Malaria	1. Quinine	10	-	No
1. S. Anaemia 2. -	1. Quinine	-	-	No

Ten patients died within the three days of follow up. All the patients who died had at least two diagnoses except two were diagnosed as having severe malaria only. They all received quinine and three of them received an antibiotic as well. One patient with suspected respiratory tract infection received quinine only and no antibiotic. Their haematocrits ranged between ten and 33 percent. Two patients did not have their haemtocrits determined. Six patients had their parasite density determined and this ranged from 2.5 to 19.3 percent.

CHAPTER SEVEN

7.0 DISCUSSION

Fever is a common symptom of malaria. It's significance in a malaria endemic area may be difficult to interpret in relation to parasitaemia. This study found that 29.4 percent of febrile children (146 out of 497 screened) between six months and five years of age presenting at the UTH, Lusaka were parasitaemic for *Plasmodium falciparum*. In a study done by Blom et al in Lusaka, Zambia (26), 21.6 percent of clinically diagnosed cases of malaria were parasitaemic on blood smear.

During the study period (January to April 1999), 5331 children aged between six months and five years were admitted to the department of paediatrics admission ward. Of these 1559 (29.2%) had a clinical diagnosis of malaria, 942 (17.7%) were diagnosed as RTI/pneumonia and 733 (13.8%)had protein energy malnutrition. Other diagnoses of significance were anaemia (6.9%) and diarrhoeal disease (10.5%) (UTH records, A-block admission).

Integrated Management of Childhood illnesses recommends that all febrile children seen at a primary health facility should receive an anti-malarial. This study found that about 70% of febrile children aged between 6 months and 5 years did not have demonstrable malaria parasitaemia on admission. This may imply that 70% of febrile children who receive anti-malarials may not actually have malaria. Though IMCI recommendations are valid in a primary health care setting, they may not apply in a hospital setting with professional staff and laboratory facilities. However, it is important to remember that malarial parasites are not demonstrable in the peripheral blood at all times. The chances of demonstrating peripheral parasitaemia are

highest when the patient has fever. It is recommended that three blood slides taken at 6 to 12 hourly intervals be examined for malaria parasitaemia before concluding that there is no parasitaemia (24). In our environment, performing at least three blood slides on every patient suspected to have malaria may not be practical and cost effective.

Other tests, such as those based on detecting histidine rich protein-2 antigen may be useful to identify cases where a blood slide is negative in a febrile patient. These tests are expensive and are not routinely available.

The duration of fever before presentation to the UTH was wide, ranging from a day to sixty days,the average being 5.4 days. The duration of symptoms before presenting to hospital may relate to the severity of the symptoms. Thus, those perceived by the care giver to be severely ill will present earlier than those perceived to be less ill. Other factors to consider, though not studied in this study, include accessibility of health services, period of time the primary health worker takes before it is decided to refer the patient to UTH and financial constraints.

The fever of falciparum malaria in the non-immune is classically a tertian fever, i.e. it occurs every second day. In this study 41.4 percent of the patients reported constant fever and 58.6 percent reported intermittent fever. In a study done in Tanzania in children aged between 0-9 years, fever was reported to have been intermittent in 98 percent of malaria cases (8).

Thirty one point seven percent of the patients had traveled out of Lusaka in the previous fourteen days. This raises the possibility of 'imported' malaria in this group.

The most common clinical features associated with falciparum malaria were anaemia, anorexia, vomiting, cough, convulsions and splenomegaly. To further define associated clinical features of significance, it would have been useful to look at similar associated features in a population of children with fever but without parasitaemia.

The low prevalence of diarrhoea in association with malaria is not surprising as this has been documented in another study (9). The very high prevalence of anaemia in this study as compared to anaemia in the general paediatric population in Zambia (65%) (21) may signify the role malaria plays in contributing to anaemia in children.

In a study done in Zaire in children aged 6 through 59 months, it was estimated that 29% of their anaemia was attributable to malaria. History of fever with splenomegaly was found to be an independent risk factor for anaemia. It was also found that parasitaemic children with a history of recent anti-malarial treatment had lower haematocrits (14). This may imply that those whose parasitaemia was high enough to cause symptoms sought treatment or those who had been ill for a long enough time took anti-malarial drugs.

Despite the fact that malaria was the first diagnosis in 60.7 percent of the cases and the second diagnosis in 24.1 percent of the cases (total of 84.8 percent), antimalarial treatment was prescribed in 97.9 percent of the cases. This implies that although malaria was not put down among the top two diagnoses, it was still thought of as a possibility. Of note is the high frequency of the clinical diagnosis of anaemia which was 37.6 percent of the second diagnoses or 29.6 percent of all the patients. This was actually an under-estimation of the problem. The only other diagnosis which occurred with relatively high frequency was pneumonia/RTI (10.3

percent of the first diagnoses). This could have been due to intercurrent infection or is a reflection of the respiratory manifestations of malaria.

A total of 132 patients had their parasite densities determined. Sixty two point one percent had parasite densities equal to or less than 5 percent. This leaves 37.9 percent of the patients with parasite densities greater than 5 percent and falling in the severe malaria category.

Although the ratio of anaemic children to non-anaemic ones in the hyperparasitaemia group (11:1) was much higher than in the group with parasitaemia of ≤ 5 (4:1), there was no significant association between parasite density and anaemia. This is in agreement with the study done by Katrina Hedberg and others in Zaire (12). This lack of association may signify the importance of duration of parasitaemia rather than parasite density at a particular point in time as the parasitised red blood cells have to be destroyed before the haematocrit can come down. However, there was a two times likelihood of hyperparasitaemic children to be anaemic compared to children with low parasite densities.

Six out of ten patients (60 percent) with cerebral malaria had parasite densities greater than 5 percent. The number of patients with cerebral malaria was however too small to draw conclusions. No significant association was found between parasite density and convulsions or parasite density and impaired consciousness. There was also no association between parasite density and outcome. Of particular note was the patient who had a parasitaemia of 53.3 percent who was well enough to be discharged by the third day. His haematocrit was 26 percent.

Although this study did not look at the baseline parasite prevalence in non-febrile children, the observed association between high parasite densities and the clinical diagnosis of malaria reiterates the concept of cut off points of parasitaemia for clinical malaria to occur. This may indicate that the fever of those patients with lower parasite densities may have been due to other conditions other than the malaria parasitaemia. Scanty or malaria parasite smear-negative malaria is also known to be associated with severe symptoms. Most of the patients appeared to have responded well to anti-malarials irrespective of the parasite densities.

In a malaria endemic region it is difficult to make a clinical diagnosis of malaria based on fever and parasitaemia as most children are parasitaemic. Fever due to other causes may be diagnosed as malaria. In such situations a cut off point of presumed significant parasite density may be useful.

As mentioned earlier, 97.9 percent of the patients received antimalarials as part of the treatment. The remaining three (2.1 percent) who did not get antimalarials had diagnoses of meningitis with a parasite density of 0.5 percent, pneumonia but parasite density was not done and pulmonary tuberculosis with a parasite density of 0.7 percent. The third patient was however reviewed the following day when the blood slide result was communicated to the attending physician who prescribed chloroquine.

Antibiotics were given in 37.2 percent of the patients. Certain antibiotics such as tetracycline, erythromycin and sulphonamides have anti-malarial activity. Their use in combination with other anti-malarials is reserved for resistant malaria. Tetracycline is not used in children less than 7 years old because of the side effect of staining of teeth (24). In this study, the high rate of use of

penicillins rather than antibiotics with some anti-malarial activity suggests their use was for suspected bacterial infection. Seventeen patients (11.7 percent) received blood transfusions. This fraction corresponds well with the fraction of patients with severe anaemia.

The overall outcome within the three days of follow up was good with 97 patients (66.9 percent) being discharged and 35 (24.1 percent) having no more fever. Most of the patients had simple malaria. Three patients (2.1 percent) did not improve or worsened and 10 died. There was no significant association between poor outcome and high parasite densities though the numbers were too small to be conclusive.

Of the 10 mortalities, 2 did not have their haematocrits determined and the rest had haematocrits ranging between 10 percent and 33 percent. The one with the haematocrit of 10 percent died before she could be transfused. Six of these patients had their parasite densities determined which ranged between 2.5 percent and 19.3 percent. They all received quinine indicating that they were being treated for severe malaria. The case fatality rate was 6.9 percent.

CHAPTER EIGHT

8.0 CONCLUSION

Malaria still remains a problem in our University Teaching Hospital with close to 30 percent of febrile children between the ages of 6 months and 5 years being parasitaemic on admission. The finding of 70 percent of febrile children without demonstrable parasitaemia on admission may justify their treatment in UTH as opposed to the primary health centre as their fever may require further investigation.

The outcome of the cases in this study was on the whole good with almost 70 percent of the patients being well enough to be discharged by the third day of admission. Mortalities were associated with severe disease including cerebral malaria and severe anaemia. The high rate of use of antibiotics (37.2 percent) may not be justifiable in the presence of a positive malaria blood slide. However the diversity of the symptomatology and the non-availability of quick laboratory results leads the individual clinician to 'over-treat' rather than 'under-treat'. Nevertheless, it is of importance not to indulge in polypharmacy in an environment of limited resources once laboratory results are available unless the clinical picture otherwise dictates.

On the other hand about 70 percent of children who receive antimalarials on the basis of fever may not be parasitaemic. In the absence of a positive malaria parasite slide, with pointers to other disease, the use of an antimalarial is not justifiable in a hospital setting. However, with the limitations of a single blood slide, this should not be the only guide but a high clinical suspicion with the exclusion of obvious illnesses.

A larger study to determine the prevalence of falciparum malaria in febrile children in the community and/or at the first level of health care would be appropriate as the University Teaching Hospital population is really a 'filtered' population. Studies utilising antigens such as HRP-2 which are present in the blood through out the parasitaemic period would be appropriate.

CHAPTER NINE

9.0 RECOMMENDATIONS

1. In a hospital setting with laboratory facilities, clinical diagnosis of malaria should be supported by laboratory diagnosis.
2. Other causes of fever should be sought for in the absence of malaria parasitaemia.
3. Use of antibiotics should be avoided in the absence of pointers to a specific bacterial infection when blood smear is positive for malaria parasites.
4. A larger study should be done in which at least three blood smears will be examined in those whose initial smears will be negative for malaria parasites.
5. Use of anti-malarials in febrile children in a hospital setting should be reserved for those with proven malaria parasitaemia whenever possible unless they present with life – threatening conditions.

CHAPTER TEN

10.0 LIMITATIONS OF THE STUDY

The laboratory part of the study was limited by human error.

Another factor is that failure to detect peripheral parasitaemia at a particular point in time doesn't necessarily mean that there are no malaria parasites.

Only one slide was performed to determine the presence of malaria parasitaemia.

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Appendix i

QUESTIONNAIRE

No: Date:

Name:

Age:

Consented by:

Duration of fever (days):

Fever constant (Yes/No):

Has child been out of Lusaka in previous fourteen days (Yes/No):

Associated features (Yes/No):

1. Fits: .....

2. Impaired sensorium: .....

3. Vomiting: .....

4. Anorexia: .....

5. Diarrhoea: .....

6. Splenomegaly: .....

7. Cough: .....

8. Difficulty in breathing: .....

Appendix ii

CONSENT FORM

STUDY TITLE: PREVALENCE OF FALCIPARUM MALARIA IN FEBRILE CHILDREN PRESENTING AT THE UNIVERSITY TEACHING HOSPITAL; LABORATORY DIAGNOSIS CLINICAL PRESNTATION AND OUTCOME

This is a study of children aged between six months and five years presenting with fever i.e. an axillary temperature of 37.5°C and above. These children will have their blood examined for the presence of malaria parasites and anaemia. Blood will be collected from a prick on the thumb and placed on two different glass slides which will be later examined for malaria parasites in the laboratory. More blood shall be collected in a small glass tube (capillary tube) and this will be examined for anaemia if the child is found to have malaria. The results of the tests will be communicated to you.

Besides the blood examination, the children will also undergo a physical examination and certain questions will be asked (using a questionnaire) in relation to the illness of the child.

Once recruited, the children will be followed up for three days or until discharge, whichever is earlier. It is not a must to consent to the study. Those refusing to take part in the study will be accorded the same type of treatment as those consenting. Withdrawal from the study at any time is allowed.

I....., of.....

.....has given consent to have my ..... (relationship) recruited in the study.

Name of patient .....

I fully understand what is involved in the study.

Signed: .....

Witness: .....

Date: .....

Appendix iii

SAMPLE SIZE CALCULATION

The sample size was calculated using the following formula:

$$\text{sample size} = Z\ \%Z\ \frac{P(100-P)}{d\%d}$$

where z =1.96, p = proportion of estimated febrile children with falciparum malaria and d = sampling error. The sampling error was estimated at 5%.