EVALUATION OF MALARIA INFECTION IN RELATION TO AGE, RESIDENCE AND DIAGNOSIS OF PATIENTS ATTENDING KIPSAMOITE DISPENSARY, NANDI NORTH DISTRICT, KENYA

BY

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Reg. No. I56/7728/2002

A Thesis Submitted in Partial Fulfilment of the Requirements for the Award of the Degree of Master of Science (Applied Parasitology) in the School of Pure and Applied Sciences of Kenyatta University

November, 2009
DECLARATION

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This thesis is my original work and has not been presented for a degree in any other university or any other award.

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We confirm that the candidate under our supervision carried out the work reported in this thesis. We have read and approved this thesis for examination

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To my wife Rhoda and children Dickens, Victrine, Brian, Emma and Zilphah whose endurance and support have guided my effort throughout the study and research period. I dedicate this thesis to my late parents Cleopar and Zilphah.
ACKNOWLEDGMENTS

I am most grateful to my University supervisors Prof. Elizabeth D. Kokwaro, and Prof. J. Ouma of Kenyatta University, Prof. Chandy C. John of the University of Minnesota, United States of America (USA), for their patience and constructive critiquing that contributed greatly to the completion and production of this thesis. My gratitude is extended to Prof. Okello Ayot and the late Prof. Romanus Okello of Kenyatta University for their guidance and encouragement during the study period.

I sincerely appreciate the financial support and encouragement from my brother Aura and his wife Jane without which this work would have not been completed. Special thanks go to Mr. Musa Otieno of Kenya Medical Research Institute for guidance in computation and data analysis. I extend my appreciation to Dr. Erick Muchiri, Head of Division of Vector Borne Diseases (D.V.B.D) for granting me study leave to pursue further studies. I am grateful for the constant critiquing and encouragement from my colleagues Abel O. Onyango, Maurice K. Komollo, Tobias Ambundo and Mr. Abdullatif Ali, the Deputy Chief Medical Laboratory Technologist.

This study was carried out in Kipsamoite Dispensary, Nandi North district with the cooperation of the Nursing Officer Mr. John Siahi, the Clinical Officer Willy Kamuren, the Public Health Technician James Chemweno and the field assistants;
Paul, Rosebellah, Gideon, Peter, Hillary, Haron, Usilah and Peter. My gratitude also goes to the patients and the entire Kipsamoite community for their cooperation during my data collection. Finally, special thanks to sister in-law Rose Owino who offered her skills in type setting the whole document.
TABLE OF CONTENTS

Page No.

DECLARATION---------------------------------------------------------------ii

DEDICATION-------------------------------------------------------------------iii

ACKNOWLEDGMENTS-------------------------------------------------------------iv

TABLE OF CONTENTS-----------------------------------------------------------vi

LIST OF FIGURES-------------------------------------------------------------x

LIST OF TABLES--------------------------------------------------------------xi

ABBREVIATIONS AND ACRONYMS-----------------------------------------------xii

ABSTRACT------------------------------------------------------------------xiv

CHAPTER ONE

1.0    INTRODUCTION--------------------------------------------------------1
CHAPTER TWO

2.0 LITERATURE REVIEW----------------------------------------------- 6

2.1 Causes of malaria--------------------------------------------------- 6

2.2 Global malaria epidemiology---------------------------------------- -- 6

2.3 Malaria endemicity in Kenya---------------------------------------- 7
2.4 Malaria transmission-----------------------------------------------
--- 9

2.5 Epidemiology of malaria in Kenya----------------------------------9

2.6 Symptoms and signs of malaria disease-------------------------------10

2.7 Life cycle of malaria parasite--------------------------------------11

2.8 Malaria prevention and control strategies--------------------------14

2.9 Treatment of uncomplicated malaria-----------------------------16
2.9.1 Treatment of uncomplicated malaria-------------------------------17

2.9.2 Treatment of severe malaria-------------------------------------20

2.10 Development of antimalarial drug resistance------------------------20
2.10.1 The emergence and spread of antimalarials drug resistance-------21

2.11 Transmission intensity and selection and spread of resistance-----22

2.12 Pattern and diagnosis of malaria----------------------------------23

2.13 Diagnosis of malaria infection-------------------------------------27
2.13.1 Symptom based (clinical) diagnosis-------------------------------27

2.13.2 Clinical misdiagnosis--------------------------------------------31
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.14</td>
<td>Use of microscope in malaria diagnosis</td>
<td>32</td>
</tr>
<tr>
<td>2.15</td>
<td>Rapid diagnostic tests</td>
<td>36</td>
</tr>
<tr>
<td>2.16</td>
<td>Immunodiagnosis and PCR-based molecular detection methods</td>
<td>39</td>
</tr>
<tr>
<td>2.17</td>
<td>Individual patient, mothers’/caretakers’ diagnosis</td>
<td>39</td>
</tr>
</tbody>
</table>

**CHAPTER THREE**

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.0</td>
<td>MATERIALS AND METHODS</td>
<td>41</td>
</tr>
<tr>
<td>3.1</td>
<td>Study area</td>
<td>41</td>
</tr>
<tr>
<td>3.2</td>
<td>Study population</td>
<td>43</td>
</tr>
<tr>
<td>3.3</td>
<td>Study design</td>
<td>44</td>
</tr>
<tr>
<td>3.4</td>
<td>Inclusion criteria</td>
<td>40</td>
</tr>
<tr>
<td>3.5</td>
<td>Exclusion criteria</td>
<td>44</td>
</tr>
<tr>
<td>3.6</td>
<td>Sample size determination</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>44</td>
</tr>
<tr>
<td>3.7</td>
<td>Sampling procedures</td>
<td>45</td>
</tr>
<tr>
<td>3.8</td>
<td>Clinical diagnosis of malaria</td>
<td>46</td>
</tr>
<tr>
<td>3.9</td>
<td>Parasitological diagnosis of malaria</td>
<td>46</td>
</tr>
<tr>
<td>3.10</td>
<td>Individual patient, mothers/caretakers diagnosis</td>
<td>47</td>
</tr>
<tr>
<td>3.11</td>
<td>Ethical consideration and clearance</td>
<td>47</td>
</tr>
<tr>
<td>3.12</td>
<td>Data management and analysis</td>
<td>48</td>
</tr>
</tbody>
</table>
CHAPTER FOUR

4.0 RESULTS---------------------------------------------------------------49
4.1 Prevalence of malaria in patients attending Kipsamoite dispensary-------49
4.2 Variation of malaria infection by age groups--------------------------50
4.3 Distribution of malaria infection within residential areas----------51
4.4 Body temperature as an indication of malaria infection-------------52
4.5 Variation of parasitaemia with malaria infection--------------------53
4.6 Correlation between parasite density and body temperature--------55

CHAPTER FIVE

5.0 DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS--------57
5.1 Discussion---------------------------------------------------------------------57
5.2 Conclusions---------------------------------------------------------------------63
5.3 Recommendations----------------------------------------------------------------64

REFERENCES------------------------------------------------------------65

APPENDIX---------------------------------------------------------------
LIST OF FIGURES

Figure

No.

1. Map of Kenya showing ecological zones of malaria endemicity---------8
2. Life cycle of human plasmodium parasite-----------------------------12
3. Map of Kabiyet Division showing the study area----------------------42
4. Prevalence of malaria by different diagnostic methods---------------50
5. Distribution of malaria infection within residential area-----------52
6. Correlation between body temperatures with parasite density--------56
LIST OF TABLES

Table No.                                           Page

No.

1. Distribution of malaria infection by age groups--------------------------------------------51

2. Body temperature and association with malaria infection---------------------------53

3. Parasitemia in relation to residential area------------------------------------------54
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT</td>
<td>Artemisinin-based combination therapies</td>
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<td>AIDS</td>
<td>Acquired immunodeficiency Syndrome</td>
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<td>EANMAT</td>
<td>East African Network of Monitoring Antimalarial Treatment</td>
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<td>GMP</td>
<td>Global Malaria Programme</td>
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<td>GoK</td>
<td>Government of Kenya</td>
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<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<td>HRP-2</td>
<td>Histidine-rich Protein-2</td>
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<td>IL</td>
<td>Interleukin</td>
</tr>
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<td>ITN</td>
<td>Insecticides-treated bed nets</td>
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<td>KEDAHR</td>
<td>Kenya Danish Health Research Project</td>
</tr>
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<td>MAF</td>
<td>Malaria Attributable Fraction</td>
</tr>
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<td>MoH</td>
<td>Ministry of Health</td>
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<td>Pf HRP-2</td>
<td><em>Plasmodium Falciparum</em> Histidine-rich Protein-2</td>
</tr>
<tr>
<td>PLDH</td>
<td>Parasite Lactate Dehydrogenase</td>
</tr>
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<td>SP</td>
<td>Sulfadoxine/Pyrimethamine</td>
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<td>SPSS</td>
<td>Statistical Programme for Social Sciences</td>
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<td>TNF</td>
<td>Tumor Necrosis Factor</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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</tr>
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<td>RBM</td>
<td>Roll Back Malaria</td>
</tr>
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<td>RDT</td>
<td>Rapid Diagnostic tests</td>
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<tr>
<td>UNAIDS</td>
<td>United Nations</td>
</tr>
<tr>
<td>UNICEF</td>
<td>United Nations Children Education Funds</td>
</tr>
<tr>
<td>WBC</td>
<td>White Blood Cells</td>
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<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
</tbody>
</table>
ABSTRACT

Malaria imposes a huge burden upon the health and economic development of tropical nations and has been identified as a major obstacle to sustainable development by the world’s poorest regions. Diagnosis of malaria still remains a major challenge towards effective case management more so in areas with limited diagnostic facilities and lack of access to skilled health personnel. Clinical diagnosis which is the most widely used approach has several limitations leading to its low sensitivity. This study was undertaken to evaluate the performance of clinical/mothers’, caregivers/individuals’ diagnosis of malaria infection using microscopy as the gold standard to determine the accuracy to support malaria case management. The disease distribution in relation to age and residence among patients attending Kipsamoite Dispensary in Nandi North district was also assessed to inform control decision making. A total of 349 patients who visited the facility during the study period were recruited. Clinical Diagnosis criteria classified 349/349 (100%) as having malaria while mothers’/caregivers’/individuals’ diagnosis classified 214/349 (61.3%) as having malaria. Microscopy detected 113/349(32.4%) as positive for malaria Parasite density distribution was analyzed by one way analysis of variance (ANOVA). There was no significant difference in mean parasite density distribution across the seven residential area categories (P=0.261). The study revealed a statistically significant association between the body temperature and malaria infection (P< 0.001). Distribution of malaria infection in the study population was analyzed by age group (<5 and >5 years) using Pearson Chi-square test. The infection distribution was significantly associated with age group; (P<0.05). The combination of mothers’ / care givers’ / individuals’ and clinical against microscopy improved the positive predictive value (PPV) of malaria diagnosis from 32.4% to 36.8%. Malaria infection was neither associated with residential areas nor parasite density but significantly associated with body temperature. The observations of this study suggest that clinical diagnosis is less sensitive compared to mothers’/ carers’ or individuals’ malaria diagnosis. There is need to improve on clinical diagnostic criteria to progress on its performance and to train and encourage mothers/caregivers/individuals on clinical symptoms of malaria to improve home management of malaria with a view to achieving the Abuja targets of Roll Back Malaria (RBM).
CHAPTER ONE

INTRODUCTION

1.1 Background

Malaria remains the most important disease among populations in tropical and sub-tropical countries. The disease imposes a huge burden upon the health and economic development of tropical nations and has been identified as a major obstacle to sustainable development by the world’s poorest regions (Gallup and Sachs, 2001). The highest endemicity of malaria is undoubtedly found in tropical Africa and causes wide spread premature deaths and suffering, imposes financial hardships on poor households, retards economic growth and undermines living standards (Craig et al., 1999; Snow et al., 1999; WHO, 2000; Gallup and Sachs 2001). Almost 90% of the global malaria burden is concentrated in the Sub-Saharan Africa, where it is directly responsible for one in five childhood morbidity and mortality (Bremen, 2001).

The magnitude of the health problem posed by malaria in Kenya is high especially in western and on the Kenyan coast. It affects almost one third of the population and is responsible for the greater number of consultations and most common reason for hospital admissions (MoH, 2001). Children under five years and pregnant mothers are at the highest risk (Snow et al., 1999). The pattern of malaria transmission seems to be changing quite rapidly with malaria epidemics being increasingly frequent even in areas which were once free from malaria.
Although malaria is both a preventable and curable disease for which many intervention strategies are available, there are very few areas in Kenya where malaria has been effectively controlled. This is due to the fact that many of the malaria control and surveillance tools are usually unaffordable, inaccessible to remote rural communities and the necessary awareness, cohesiveness, stability and management skills to apply them are similarly deficient (Karanja et al., 2002). One area that lends itself particularly well to community participation is the diagnosis and treatment of malaria at village level (Okanurak, 1986).

The malarial disease occurs at high frequency and varies in relation to age and space (Kwadwo et al., 2003). Although treatment has been given on the basis of presumptive diagnosis of malaria, emphasis on microscopic diagnosis has received increased interest as the gold standard for malaria diagnosis (WHO, 1986; MoH, 2003).

Useful epidemiological data based on records of self reported illness or on blood smear examination can be collected at relatively little additional costs. Lack of information relating to self reported cases suggest that a change in approach is required to empower/strengthen mothers and caregivers’ in diagnosis and home management of malaria when prompt treatment at a health facility is impossible.
It is not known whether all cases clinically diagnosed and treated as malaria at this dispensary are accurate.

Furthermore, it is not known whether mothers/caretakers of sick children and individual patients have experience in accurately diagnosing malaria. The concept of home management of malaria is one of the strategies the Roll Back Malaria initiative is recommending to reduce the burden of malaria especially in children less than five years of age in Africa (Mary et al., 2001). The objective of this study was to evaluate malaria infection in relation to age, residence and diagnosis of patients attending Kipsamoite Dispensary.

1.2 Statement of the problem and justification
Malaria is one of the major health problems affecting the poor rural communities in Africa where over 90% of deaths occur with 25% being children below the age of five years (Gallup and Sachs, 2001; WHO, 1986). Malaria is a common cause of fever and illness in endemic areas (Marsh, 1996), however it is not possible to apply any one set of clinical criteria to the diagnosis of all types of malaria in all patients population. One of the strategies recommended by the WHO to reduce mortality and morbidity due to malaria especially in children below the age of five years is to encourage mothers to be able to recognise malaria signs and symptoms and manage uncomplicated malaria at household level using first line antimalarial drugs. This is in tandem with Roll Back Malaria initiative and the
Abuja declarations emphasizing the need to manage fever due to malaria within 48 hours of onset (MoH, 2001).

The delay in accessing treatment in formal health facilities during illness episodes in most African countries is major challenge to the attainment of the Abuja targets. Concordance in both the clinical and mothers’/caregivers’ diagnosis when compared to microscopy (Gold standard) could lead to further encouragement of both approaches to malaria diagnosis with a view to bridging the gap of accessibility to prompt malaria case management. There is therefore a need for an evaluation of the clinical diagnosis commonly practiced in the health facility as well as self-reported diagnosis by mothers/ caretakers, and individual patients. The non-specificity of clinical presentation of malaria coupled with lack of resources and insufficient access to trained health care providers presents diagnosis problems which hinders effective malaria case management.

1.3 Research questions

i. How accurate is the diagnosis of malaria by mothers/caretakers, individuals, clinical officer/ nurse compared to conventional microscopy method?

ii. To what extent is malaria infection distributed in relation to age and residence of patients attending Kipsamoite dispensary?

iii. What is the prevalence of malaria infection within the study population?
1.4 Hypotheses

i. Mother’s/caretaker’s or clinical Officer’s/nurse’s diagnosis of malaria do not vary significantly when tested against microscopy.

ii. Malaria infection in the study population is not age related.

iii. Prevalence of malaria infection within the study population does not vary.

1.5 Objectives of the study

1.5.1 General objective

To evaluate malaria infection in relation to age, residence and diagnosis of patients attending Kipsamoite dispensary, North Nandi District, Kenya.

1.5.2 Specific objectives

i. To determine the prevalence of malaria infection among patients attending Kipsamoite dispensary.

ii. To determine the distribution of malaria infection in the study area.

iii. To identify the age-specific distribution of malaria infection among the study population.

iv. To evaluate the diagnosis of malaria by mothers/care takers/individuals and clinical officer/nurse using microscopy as the gold standard.
CHAPTER TWO
LITERATURE REVIEW

2.1 Causes of malaria

Malaria is caused by infection of red blood cells with protozoan parasites of the genus *Plasmodium*. The parasites are inoculated into the human host by a feeding female anopheline mosquito. The four *Plasmodium* species that infect humans are *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malariae*. Occasional infections with monkey malaria parasites, such as *Plasmodium knowlesi*, also occur (MoH, 2006).

2.2 Global malaria epidemiology

Currently more than 40% of the world’s populations live in areas of high malaria risk and the great majority are found in Sub-Saharan Africa (WHO, 2000). Malaria occurs in more than 100 countries throughout Africa, Central and South America, Asia, Haiti, Dominican Republic and Turkey (WHO, 1996). An estimated 500 million clinical cases are reported each year with over 2.6 million deaths worldwide. Over 90% of these deaths occur in Africa with 25% of deaths in children below the age of five (WHO, 1996). However, worst effects of the disease are felt in the sub-Saharan Africa where it undermines the health and
welfare of families, endangers the survival and education of children, causes disabilities and impoverishes individuals and countries (WHO, 2000).

2.3 Malaria endemicity in Kenya

Malaria is a priority disease in Kenya accounting for 30% of outpatient hospital attendance nationally and 19% of all admissions to health facilities of which 5% die (Snow et al., 1998b). The level of endemicity of malaria in Kenya ranges from region to region. Malaria endemicity ranges from hyper-endemic to holo-endemic areas at the coastal and Lake regions of Kenya respectively (Figure 1). Unstable malaria also occurs in several areas of Kenya, which include Kajiado, Narok and arid and semi-arid areas (MoH, 2003). Epidemic malaria occurs in most western Kenya highlands, which include Kisii, Nyamira, Trans-nzoia, and Nandi (Hay et al., 2002).
Figure 1: Map of Kenya showing Ecological Zones of malaria endemicity

(MoH, 2008)
2.4 Malaria Transmission

The number and species of Anopheline mosquitoes determine to a large extent the level of transmission in a given area. Malaria transmission is influenced by climate and geography and often coincides with the rainy season (Craig et al., 1999), when breeding sites are available with high numbers of Anopheles mosquitoes.

Population movements also contribute to the spread of malaria and movement of infected people from areas where malaria is endemic to areas where the disease has been eradicated has led to the resurgence of disease (Prothero, 1977). Deforestation for resettlement and creation of irrigation schemes also increase the risk of transmission (John et al., 2004).

2.5 Epidemiology of malaria in Kenya

The epidemiology of malaria transmission and the severity of the disease vary greatly from region to region, village to village and even from person to person within a village (Guyatt et al., 2001). Some of the differences are due to the particular malaria parasite species. *Plasmodium falciparum* is the most common species of malaria parasite found in the highlands, while *Anopheles gambiae* complex is the most common vector species. Currently it is estimated that 25% of the total population of Kenya (7,823,000) is at the risk of malaria epidemics (WHO, 2003).
Knowledge of cause of morbidity and mortality is also important in assessing the results of intervention campaigns directed against diseases such as malaria. The Kenyan government has recently defined 16 districts in the western Kenya highlands (MoH, 1999; Hay et al., 2002), as being prone to epidemics meriting close inspection, preparation and intervention (MoH, 2001). Severe malaria due to infection with \textit{P. falciparum} often leads to death in absence of prompt medical intervention. Malaria during pregnancy can also cause miscarriage, fetal death, and intrauterine growth retardation, low birth weight and premature delivery (Guyatt et al., 2001; Steketee, 2001).

2.6 Symptoms and signs of malaria disease

The first symptoms of malaria are nonspecific and similar to the symptoms of a minor systemic viral illness. They comprise: headache, lassitude, fatigue, abdominal discomfort, muscle and joint aches, followed by fever, chills, perspiration, anorexia, vomiting and worsening malaise. This is the typical picture of uncomplicated malaria. Residents of endemic areas are often familiar with this combination of symptoms, and frequently self-diagnose. Malaria is therefore frequently over diagnosed on the basis of symptoms alone. Infection with \textit{P. vivax} and \textit{P. ovale}, more than with other species, can be associated with well-defined malarial paroxysms, in which fever spikes, chills and rigors occur at regular intervals.
At this stage, with no evidence of vital organ dysfunction, the case-fatality rate is low (circa 0.1% for *P. falciparum* infections – the other human malarias are rarely fatal) provided prompt and effective treatment is given. If ineffective drugs are given or treatment is delayed in *falciparum* malaria, the parasite burden continues to increase and severe malaria may ensue. A patient may progress from having minor symptoms to having severe disease within a few hours. This usually manifests with one or more of the following: coma (cerebral malaria), metabolic acidosis, severe anaemia, and hypoglycemia in adults, acute renal failure or acute pulmonary edema. Usually at this stage, mortality in people receiving treatment has risen to 15–20%. If untreated, severe malaria is almost always fatal (MoH, 2006).

### 2.7 Life cycle of malaria parasites

Plasmodia which cause malaria infection in humans include *P. falciparum, P. vivax, P. ovale* and *P. malariae*. Human infection with *Plasmodium* begins when the malaria vector, a female *Anopheles* mosquito, inoculates plasmodia sporozoites from its salivary glands into human during a blood meal. The sporozoites mature in the liver and are released into the blood stream as merozoites (MoH, 2006). These invade red blood cells, causing fever. Some forms of the parasites (gametocytes) are ingested by the *Anopheles* mosquitoes during feeding and develop into sporozoites restarting the cycle (Figure 2). The pathological changes in malaria are related to the development of asexual parasites in the blood.
The release of malaria antigens, pigment and toxins gives rise to a cascade of pathological events. Among these the production of cytokines, particularly tumor necrosis factor (TNF), induced by the release of parasite products during schizont rupture, appears to play a central role; complemented by the effects of other circulating “endogenous pyrogens” such as interleukin-1 (IL-1) and IL-6 (Snow et al., 2006).
Tumor Necrosis Factor or cachexin has been implicated as the cause of malarial fever. Although the nature of malarial toxin is still controversial, it is generally agreed that it is released at the time of schizont rupture (Pasvol, 2006).

In spite of the many forms of malignant tertian malaria that are known, death from *P. falciparum* in children living in areas of stable malaria is usually due either to cerebral malaria, malarial anaemia, metabolic acidosis, or a combination of these; whereas death in non-immunes are often associated with acute renal insufficiency, cerebral malaria, pulmonary edema and disseminated intravascular coagulation (Menendez *et al.*, 2001).

All clinical attacks of malaria are associated with red cell destruction, and thus a degree of anaemia. This is arbitrarily considered to be severe if the haemoglobin concentration is less than 5 g/l (Menendez *et al.*, 2001). Severe anaemia forms a large part of the morbidity due to *P. falciparum* infection in Africa. In addition to the loss of red cells due to parasite invasion there is also considerable destruction of uninfected red blood cells (Srivicha, 2007).

A range of potential mechanisms, including immune sensitisation and damage by oxygen radicals have been advanced to explain this (Lartey, 2000). At the same time it has been reported that malaria infection leads to dyserythropoiesis and hypothesized mechanisms include suppression by chronic release of cytokines.
such as TNF (Clark, 2006). These findings have led to the idea that malarial anaemia may be a chronic process as well as an acute event (Lartey, 2000); and in a sense this is undoubtedly true in that it has often been demonstrated that the mean haemoglobin of childhood population rises following successful control of malaria.

In the placenta, developing trophozoites are numerous in the intervillous spaces and are found in the greatest numbers next to the trophoblast of the stratum spongiosium, and haemozoin may be seen within the fibrin masses. The maternal blood in the intervillous spaces is high in glucose content-favouring the development of the parasite (WHO, 1996). The mechanism by which placenta parasitisation affects foetal growth is not known.

2.8 Malaria prevention and control strategies
Malaria situation in the tropical and sub-tropical regions calls for development of the new methods and utilisation of available control strategies. Over the past few decades a number of interventions are being promoted in malaria endemic regions of the world to reduce malaria burden. In nearly all situations, vector control is the main measure to prevent malaria transmission.
The WHO recommends integrated vector management as a systematic approach to selecting the best method of vector control or combination of methods to reduce transmission. Indoor residual spraying, which kills mosquitoes inside houses, has in the past played a major role in the elimination of malaria from many countries and is still an important method, especially for preventing epidemics. Insecticide-treated mosquito nets also prevent malaria transmission and child deaths due to malaria. Large-scale controlled trials of insecticide-treated bed nets (ITN’s) has shown a reduction of malaria mortality in the < 5 year old children. They have also proven effective for the reduction of malaria incidences in other parts of the world. Arising from the combined evidence of five-trial settings, it appears that in short term, reducing infection risk leads to an immediate impact in both high and moderate transmission areas (Snow and Marsh, 2002; http://www.rollbackmalaria.org/partnership.itn/docs/cochraine-review, 2004).

On the average, ITN usage averts approximately six out of one hundred deaths among children < 5 years old and this impact appears to be reasonably similar irrespective of transmission intensity. The proportional reduction in mortality tends to be higher in the low transmission/low-mortality sites since the same average 6-child lives saved constitute a larger proportion of a generally lower overall mortality rate (Snow and Marsh, 2002). On the Kenyan Coast, an area where children will receive between 1-10 new infection each year (WHO, 2000), ITN reduced the incidence of malaria infection among children by 50% (Snow et
al., 1997), which resulted in a reduction in all-cause mortality among children 1-59 months old by 30%, 3.8 lives per 1000 child-years (WHO, 2005).

In areas of intense malaria transmission where children can expect to receive on average 60-300 infective bites per person/year at Asembo Bay near lake Victoria, ITNs reduced the incidence of new malaria infections among children by 74% (Snow et al., 1997). Although several studies have shown that insecticide-treated bed nets can reduce parasitemia (Talisuna and Meya, 2007), clinical attacks and mortality (WHO, 2005), they still have little widespread use. The situation is worsened currently by lack of a vaccine (Sharma and Pathak, 2008).

2.9 Treatment of malaria

Prompt access to effective treatment is one of the key interventions promoted by Global Malaria Programme (GMP) and can be done by administration of drugs to persons showing signs of malaria in malaria-endemic areas. The antimalarial drugs attack the *Plasmodium* parasites in the blood. However, the control of malaria has been met with some challenges. One of the major obstacles has been the development of resistance to drugs by malaria-causing parasite *P. falciparum*. Chloroquine, which is a cheap drug and one that has been mostly widely used, has lost its clinical effectiveness while sulfadoxine/pyrimethamine (SP) is also becoming ineffective (WHO, 2003). Artemisin based combination therapies
(ACTs) are the latest ant-malarial drugs which are highly effective but are much more expensive.

2.9.1 Treatment of uncomplicated malaria

The recommended first line treatment of uncomplicated malaria in Kenya is artemether-lumefantrine, currently available as a co-formulated tablet containing 20 mg of Artemether and 120 mg of lumefantrine (MoH, 2006). This is administered as a 6-dose regimen over three days. Malaria patients with HIV/AIDS should be managed according to the same regimen above. In children below 5 kg (under 2 months of age) malaria is not a common cause of fever. Evaluation of other causes should be undertaken. Where malaria is diagnosed the recommended treatment is oral quinine. The recommended second line treatment drug for uncomplicated malaria in Kenya is oral quinine (MoH, 2006).

Despite the significance of reducing the risks of infection through insecticide-treated bed nets, many believe that the foundation to any successful efforts to reduce the mortality burden posed by malaria will be through prompt and effective case-management of febrile illness (Snow and Marsh, 2002; Trape et al., 2002). While this seems to be an apparently simple strategy, the majority of the African continent has a number of distinguishing features, which make this approach complex. Malaria is a common illness, most frequently occurring as a minor
illness, especially among immune adult populations. It may not therefore be perceived as a high-risk disease. Diagnosis of malaria is difficult; resources to make a parasitological diagnosis, and algorithms to interpret the findings, present management problems, especially in endemic settings (Chandramohan et al., 2001). At the same time, early death or deterioration are common features of malaria cases that progress to severe illness, implying a narrow window of opportunity for instituting effective treatment in these most severe cases (Greenwood et al., 1987).

The greatest burden of disease occurs in resource-poor environments, where geographic access to government health facilities is limited, and both regulatory and communication strategies compromised. This commonly leads to inappropriate treatment strategies being adopted, for those seeking treatment through the further compromised regulatory strategies, and lead to widely varying quality amongst available antimalarial drugs, especially within the private retail sector (Tipkei, 2008).

Additional complications derive from emerging antimalarial drug resistance, and the lack of cheap, safe, and efficacious replacements. The basic premise that appropriate case-management will result in demonstrable gains in child survival depends critically upon whether the right drug (safe, efficacious and of acceptable quality) is administered at the correct dose as early as possible in the disease event
and that treatment courses are completed (Goodman et al., 2001). African heads of state met in Abuja in April 2000 and agreed, as part of the RBM movement; ensure that at least 60% of all fevers would be managed this way by the year 2010 (WHO, 2000b).

In most studies, treatment seeking for fevers is described as a hierarchical process where caretakers or patients first seek cheaper alternatives before progressing to the formal sector in the course of the illness (Nyamongo, 2002). Studies undertaken at formal public facilities have also shown that a high proportion of fevers are first treated at home with shop-bought antimalarials and antipyretics before presenting to the health facility (Snow et al., 1992). It is also acknowledged that caretakers’ responses to questions on health seeking are not always accurate.

Treatment with antimalarial drugs has been the most widely used efforts to reduce the effect of malaria in Africa (WHO, 1996). However, treatment provided through health centers and health posts has been of little help in reducing deaths in infants and young children because severe P. falciparum malaria in these children strikes so rapidly that mothers are not able to obtain treatment in time (Mwabu, 1986; Reubesh et al., 1995).
2.9.2 Treatment of severe malaria

In all patients with suspected severe malaria with or without fever or history of fever, the use of parasitological diagnosis is recommended. However, antimalarial treatment should not be withheld if parasitological diagnosis is not possible. The recommended medicine of choice for severe malaria is parenteral quinine. The preferred route for administration is intravenous route. However, the intramuscular route can be used as an alternative where intravenous route is not possible (MoH, 2006).

2.10 Development of anti malarial drug resistance

Antimalarial drug resistance is the ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended, but within the limits of tolerance of the subject (WHO, 1973). The evolution of drug resistance in Plasmodium is not fully understood although the molecular basis is becoming clearer. The development of resistance to chloroquine probably requires successive genes mutation and evolves slowly. Recent evidence indicates that for P. falciparum some of these mutations occur in atranspoter: - like gene on the surface of the parasite food vacuole (Su, 1997).
2.10.1 The emergence and spread of antimalarial resistance

The development of resistance can be considered in two parts: the initial genetic event, which produces the resistant mutant and the subsequent selection process in which the survival advantage in the presence of the drug leads to preferential transmission of resistant mutants and thus the spread of resistance (Peters, 1987). In the absence of the antimalarial, resistant mutants may have a survival disadvantage. This “fitness cost” of the resistance mechanism may result in a decline in the prevalence of resistance once drug pressure is removed (Su, 1997).

Resistance to one drug may select for resistance to another where the mechanisms of resistance are similar (cross-resistance). There are many parallels with antibiotic resistance, in particular resistance to antituberculosis drugs where, as for malaria, transferable resistance genes are not involved in the emergence of resistance (White, 2004). In experimental models, drug-resistant mutations can be selected without mosquito passage (without meiotic recombination) by exposure of large numbers of malaria parasites (either in vitro, in animals, or as was done in the past, in volunteers) to subtherapeutic drug concentrations (Peters, 1987).

Various factors determine the propensity for antimalarial drug resistance to develop (White et al., 1999). The emergence of resistance can be thought of in terms of the product of the probabilities of new emergence (a rare event) and subsequent spread. Resistant parasites, if present, will be selected when parasites
are exposed to “selective” (sub therapeutic) drug concentrations. “Selective” in this context means a concentration of drug that will eradicate the sensitive parasites but still allow growth of the resistant parasite population such that it is eventually transmitted to another person. Since new resistance arises randomly among malaria parasites, non-immune patients infected with large numbers of parasites who receive inadequate treatment (either because of poor drug quality, poor adherence, vomiting of an oral treatment, etc.) are a potent source of new resistance (White, 2004).

The subsequent spread of resistant mutant malaria parasites is facilitated by the widespread use of drugs with long elimination phases. These provide a “selective filter”, allowing infection by the resistant parasites while the residual antimalarial activity prevents infection by sensitive parasites (Su, 1997). Slowly eliminated drugs such as mefloquine (terminal elimination half-life (T1/2β 2–3 weeks) or chloroquine (T1/2β 1–2 months) persist in the blood and provide a selective filter for months after drug administration has ceased.

2.11 Transmission intensity and the selection and spread of resistance

The recrudescence and subsequent transmission of an infection that has generated a new resistant malaria parasite is essential for resistance to be propagated (White et al., 1999). Gametocytes carrying the resistance genes will not reach transmissible densities until the resistant biomass has expanded to numbers close
to those producing illness (>10^7 parasites) (Van geetruyden et al., 2008). Thus to prevent resistance spreading from an infection that has generated new resistance, gametocyte production from the recrudescent resistant infection must be prevented. In high-transmission areas, the majority of infections are asymptomatic and infections are acquired repeatedly throughout life. Symptomatic and sometimes fatal malaria occurs in the first years of life, but thereafter it is increasingly likely to be asymptomatic (Roper et al., 2004).

This reflects a state of imperfect immunity (premunition), where the infection is controlled, usually at levels below those causing symptoms. The rate at which premunition is acquired depends on the intensity of transmission. In the context of intense malaria transmission, people still receive antimalarial treatments throughout their lives (often inappropriately for other febrile infections), but these “treatments” are largely unrelated to the peaks of parasitaemia, thereby reducing the probability of selection for resistance. Immunity considerably reduces the emergence of resistance (Roper et al., 2004).

2.12 Pattern and diagnosis of malaria

In common with most infectious diseases, malaria distribution within a geographical area is heterogeneous and can vary greatly between villages and house holds (Gamage-Mendis, 1991; Carter et al., 2000). These patterns of malaria reflect a composite of heterogeneities in vector distribution, human-
vector contact and human host factors. Identified risk factors for malaria include distance to known mosquito breeding sites, household constructions, household crowding and personal protection measures against mosquito biting (Killen and Smith, 2007; Freedman, 2008).

Kleinschmidt and Sharp in 2001 demonstrated that age-specific incidence varied considerably in areas of high incidence and in years of high incidence. In these areas malaria incidence rose with age until the late teens and either remained constant or reduced in young adults. This finding appears to be consistent with results from settings of much higher transmission intensities which show that clinical tolerance to infection with *P. falciparum* in adults may be acquired as a result of small number of infective bites in early childhood and implies that even in this relatively low transmission area, there is an asymptomatic reservoir of infection in older people. The results also show that in high incidence sub-regions the lowest incidences are reported for children less than 5 years of age, which may be the results of greater protection offered to this age group by malaria vector control through indoor house spraying.

The relationship between the patterns of age specific malaria morbidity and malaria transmission intensity has been well documented (Snow *et al.*, 1997). The pattern of age-specific malaria incidence can therefore serve as an indication of the presence of naturally acquired immunity in a population. A study in Northern
Ghana revealed significant differences in parasitaemia and anaemia that correlate with seasonal malaria conditions, age, place of residence and measured fever (Kwadwo et al., 2003). Although symptoms associated with Plasmodium infection in non-immune are likely to be more severe, a study of fever and malaria in highland Uganda (Lindblade et al., 1999) suggested that they are relatively non-specific. Use of combination of symptoms did not significantly improve the sensitivity and specificity of clinical malaria diagnosis in this highland region as compared with diagnostic algorithms in endemic transmission areas (Olaleye et al., 1988). Observed fever was not a good indicator of malaria, although documented fever (observed or history) was highly sensitive. In areas of low immunity for malaria, it is arguably more important to use highly sensitive diagnostic criteria and treat all probable cases of malaria given the life threatening nature of the disease. Lower transmission of malaria in non-endemic areas is likely to result in relatively fewer fever cases due to malaria (Muhe et al., 1999) so that presumptive treatment for fever may result in significant overuse of anti-malarial drugs and improper management of other febrile illnesses.

In Gambia, mothers of seriously ill children were shown to give accurate diagnosis of their children’s illnesses at the time of presentation at hospital. The mothers’ initial and final diagnosis corresponded with laboratory and clinical diagnosis 76% and 88%, (Alonso et al., 1987). A study by Deressa and Enquesellasia, (2003) in rural communities in southern Ethiopia, indicated that
self-treatment at home is the major action taken to manage malaria. Therefore efforts should be made to improve the availability of effective antimalarials to communities in rural areas with malaria through mother coordinators, drug sellers and shop owners.

Another study of childhood morbidity surveillance in lowland Kenya (Bondo district) also revealed mothers’ diagnosis showing significant sensitivity of 52.3% and specificity of 58.3% while clinician’s diagnosis showed 73% sensitivity and 44% specificity (Kenya Danish Health Research Project-KEDAHR-report, 1998). In western Kenya, a survey of home treatment of children with fever, bed net use and attendance at ante-natal clinics showed that caretakers are major prompt providers of antimalarial treatment (Mary et al., 2001), and home treatment practices should be strengthened and endorsed when prompt treatment at a health facility is impossible. In the same study, it was also shown that high-level utilization of antenatal clinics provides the opportunity to achieve good coverage with presumptive intermittent treatment for malaria during pregnancy. In Kipsamoite dispensary, it is not known whether all cases clinically diagnosed and treated as malaria are accurate and whether mothers/caretakers have the experience of accurately diagnosing malaria. It is also not known if the pattern of malaria is uniform in relation to age and place of residence.
This study therefore investigated the age distribution, residence specific pattern of malaria infection and its diagnosis in patients attending Kipsamoite dispensary. Any variation that may warrant special consideration in implementation of intervention measures was evaluated and the reliability of the clinician’s and mothers’/caretakers’ diagnosis determined.

2.13 Diagnosis of malarial infection

In high malaria endemic areas of Kenya, any child with fever or history of fever should be presumptively classified and treated as malaria. The use of parasitological diagnosis is not a pre-requisite for treatment. In low malaria endemic areas, any child with fever or history of fever in the absence of measles, running nose or any identifiable cause of fever should be presumptively classified and treated as malaria. The use of parasitological diagnosis is recommended where possible. In all patients five years and above with fever or history of fever, in the absence of any obvious cause of fever, the use of parasitological diagnosis is recommended (MoH, 2006).

2.13.1 Symptom-based (clinical) diagnosis

The signs and symptoms of malaria, such as fever, chills, headache and anorexia are non-specific and are common to many diseases and conditions. Malaria is a common cause of fever and illness in endemic areas (Marsh et al., 1995), but it is
not possible to apply any one set of clinical criteria to the diagnosis of all types of malaria in all patient populations.

The appropriateness of particular clinical diagnostic criteria varies from area to area according to the intensity of transmission, the species of malaria parasite, other prevailing causes of fever, and the health service infrastructure (WHO, 2000). One of the factors leading to a change in the clinical epidemiology of malaria in some areas is the prevalence of HIV/AIDS.

This disease can increase the risk of acquiring malaria or the progression to severe malaria, depending on malaria transmission in the area and the age of the patient. The prevalence of HIV/AIDS can also lead to an increase in the incidence of febrile disease that is not malaria, and can therefore cause further difficulties in the symptom-based diagnosis of malaria (Nuanyanwu et al., 1996). Two different studies in the Gambia have shown that a sensitivity of 70–88% and a specificity of 63–82% for malaria diagnosis could be achieved using a weighting and scoring system for clinical signs and symptoms (WHO, 2006).

These methods may be too complicated to implement and supervise under operational conditions in the field, and many of the key symptoms and signs of malaria in one area may not be applicable elsewhere. For instance, reduced
feeding in a child is more likely to indicate malaria in the Gambia than in Ethiopia (Bojang et al., 2000).

Fever alone is as effective a criterion for diagnosis as clinical algorithms; a review of 10 studies indicated that use of the more restrictive criteria of clinical algorithms resulted in only trivial savings in drug costs compared with use of a fever-based diagnosis, even in areas of low malaria prevalence. In areas of high prevalence it greatly increases the probability of missing malaria infections (Chandramohan et al., 2002).

In view of high prevalence of malaria infections and the non-specific signs and symptoms of the disease, the diagnosis of clinical malaria presents difficult methodological problems in highly endemic areas (Marsh, 1992; Greenwood et al., 1987). The onset of a *P. falciparum* attack is often insidious, with any of a range of non-specific symptoms, and temperature variation during the acute attack does follow the classic intermittent pattern described for non-immune individuals (Harinasuta and Bunnag, 1998). Normal body temperatures in tropical Africa vary with age and even with the time of day (Armstrong et al., 1994). Febrile temperatures in young children are frequently the result of causes such as respiratory infections and are not necessarily a consequent of malaria even when the patient is parasitaemic.
Despite the consequent uncertainties in the diagnosis of individual malaria cases in endemic areas, it is possible to estimate the proportion of fever cases that are malaria-attributable using parasitaemia data, assuming that the risk of symptomatic malaria increases with parasite density. The application of this approach to community survey data from highly endemic area of Tanzania had been demonstrated (Smith et al., 1994b).

The malaria-attributable fraction (MAF) is the proportion of morbidity that would be removed if malaria were eliminated. In the past, these difficulties have proven a major obstacle in the evaluation of malaria control strategies, and presently the same difficulties are being encountered in attempts to estimate the efficacy of recently developed malaria vaccines. To estimate the fraction of fever cases due to malaria, methods based on the measurement of the parasite density have been developed in recent years (Snow and Marsh, 1988a; Smith et al., 1994b).

However, the intrinsic nature of the relationship between parasitaemia and fever at the individual level has never been investigated nor has the variations in tolerance of parasitaemia among individuals, and there is no consensus of opinion as to what criteria define a clinical episode of malaria (Rougemont et al., 1991; Cox et al., 1994). Although treatment has been given on the basis of presumptive diagnosis of malaria, emphasis on microscopic diagnosis has received increased interest as the gold standard for malaria diagnosis (WHO, 1986; MoH, 2003).
2.13.2 Clinical misdiagnosis

Providing health care in resource-limited setting is admittedly a complex problem, and for clinics or district hospitals with minimal-to-no laboratory support, diagnoses are often made clinically (e.g., by use of clinical algorithms for malaria and tuberculosis). Reliance on clinical diagnosis is attractive in areas with a high prevalence of disease, incurs no extra cost, and requires no special laboratory equipment or supplies, however, diagnoses based on clinical signs and symptoms can be non-specific, unreliable and associated with increased mortality (Makani et al., 2003).

Among 4,670 patients admitted to Tanzanian hospitals who received the clinical diagnosis of severe malaria by World Health Organization (WHO) criteria, <50% had a blood smear result confirming the presence of *Plasmodium falciparum* (Reyburn et al., 2004). Patients with parasites found on blood smears had better outcomes than did patients without laboratory evidence of malaria, which suggests that other serious illnesses were not considered as severe or perhaps dismissed in favour of malaria (Makani et al., 2003; Reyburn et al., 2004; Evans et al., 2004). In a retrospective analysis of children at a tertiary referral centre in Kumasi, Ghana, 40% of patients who had been given a WHO–defined clinical diagnosis of malaria were confirmed to actually have bacterial sepsis (Evans et al., 2004).
Clearly, the absence of laboratory support contributes to an over diagnosis of malaria that leads to a failure to treat or a delay in treatment of alternative life-threatening infections and potentially increases mortality (Amexo et al., 2004). Clinical overlap between diseases is another common problem that may potentially compromise patient care and that may result in inappropriate antimicrobial therapy (O’Dempsey et al., 1993; Snow et al., 1992).

Understandably, allocation of resources (human and economic) to diagnostic laboratory testing has not been a priority for resource-limited health care systems, and over-stretched laboratory staff with limited supplies are often reluctant to perform quality control on a routine basis. However, unreliable and inaccurate laboratory diagnostic testing leads to unnecessary expenditures in a region already plagued by resource shortages, promotes the perception that laboratory testing is unhelpful, and compromises patient care. All those factors underscore the need for an external assessment system to monitor laboratory and test performance.

2.14 Use of microscope in malaria diagnosis

In addition to providing a diagnosis with a high degree of sensitivity and specificity when performed well, microscopy allows quantification of malaria parasites and identification of the infecting species. It is inexpensive, the cost varying from US$ 0.40–0.70 per slide and is considered to be the “gold standard” against which the sensitivity and specificity of other methods must be assessed. A
skilled microscopist is able to detect asexual parasites at densities of fewer than 10 per µl of blood but under typical field conditions the limit of sensitivity is approximately 100 parasites per µl (WHO, 2000).

Light microscopy has several important advantages including low direct costs if the infrastructure to maintain the service is available, high sensitivity if the quality of microscopy is high, differentiation between plasmodia species, determination of parasite densities and can be used to diagnose many other conditions. Understandably, allocation of resources (human and economic) to diagnostic laboratory testing has not been a priority for resource-limited health care systems, and over-stretched laboratory staff with limited supplies are often reluctant to perform quality control on a routine basis. For sub-Saharan Africa, the WHO has designated malaria microscopic evaluation and haemoglobin, glucose, and HIV testing as essential laboratory services. However, unreliable and inaccurate laboratory diagnostic testing leads to unnecessary expenditures in a region already plagued by resource shortages, promotes the perception that laboratory testing is unhelpful, and compromises patient care. A recent report from Ghana of the success of nationwide technician training programme highlighted not only the reality of inaccurate test results but also the potential for improvement through an organized initiative (Bates et al., 2004). Similarly, the Malaria Control Program in South Africa discovered significant disagreement between laboratories in the microscopic examination of Giemsa stained thick blood smears (Durrhelm et al.,
Numerous attempts have been made to improve malaria microscopy, but none has proven superior to the classical method of Giemsa-staining and oil-immersion microscopy for performance in typical health-care settings (Clinton et al., 2003). All those factors underscore the need for an external assessment system to monitor laboratory and test performance.

It can be difficult to maintain good quality of microscopy, for various reasons such as the need for adequate training and supervision of laboratory staff, the need to rely on electricity at night times, delays in providing results to patients and the need for maintaining quality assurance and control of laboratory services. Numerous attempts have been made to improve malaria microscopy, but none has proven superior to the classical method of Giemsa-staining and oil-immersion microscopy for performance in typical health-care settings (Clinton et al., 2003).

Each year in sub-Saharan Africa, 12 million people die (UNICEF, 2005), and, for the majority of individuals, the causes of death are largely uninvestigated. These uninvestigated deaths are generally attributed to infectious disease (WHO, 2004), most commonly HIV infection, malaria, and tuberculosis, but, in the absence of laboratory confirmation, the accuracy of these estimates remains uncertain. In fact, a recent study from Kenya found that bacterial bloodstream infections diagnosed by blood culture were responsible for 26% of deaths among children (Berkley et al., 2005), which suggests that invasive bacterial infections
may be an underappreciated cause of death. With 25 million people with HIV/AIDS disease in the African region (UNAIDS, 2004), the burden of infectious disease is even more patent. Quality laboratory testing is crucial to confirm clinical diagnoses, conduct accurate infectious disease surveillance and direct public health care policy. However, in this time of crisis, the current laboratory and health care infrastructures are insufficient to meet these needs and perhaps have been ignored.

To date, the vast majority of financial resources from funding organizations have been focused on disease prevention and provision of care, whereas relatively little funding has been allocated to build laboratory capability (Clinton et al., 2003). Furthermore, because access to reliable diagnostic testing is severely limited or undervalued, misdiagnosis commonly occurs, resulting in inadequate treatment, increased mortality and an inability to determine the true prevalence of diseases.

Two landmark studies published recently have contributed significantly to the understanding of aetiology of febrile illness in Kenya and Burkina Faso and demonstrate the need for physicians to consider alternative diagnoses in their clinical practice (Berkley et al., 2005; Mulholand and Adegbola, 2005; Parent du Chatelet et al., 2005). However, the laboratory means to identify these infections are routinely unavailable, and investigators frequently neglect the importance of diagnostic testing (Benatar, 2004) or fail to emphasize the need for parallel
development of laboratory testing for non-research purposes. In the recent time, laboratory expenditures have been prohibitive for many countries in this region, where 38% of the population lives on <US$ 1 a day and the gross national income per capita is US$ 496 (UNICEF, 2005). The challenge remains, therefore, to develop affordable and sustainable laboratory infrastructures to support the diagnosis of infectious diseases. Still, the barriers to laboratory testing in sub-Saharan Africa are protean, are unique between and within countries and extend far beyond economic constrains. Health care policy makers and clinical investigators need to promote rational, cost-effective diagnostic methods for infectious diseases, with an emphasis on improving the overall health care delivery system. Central to renewed efforts to Roll-Back Malaria (RBM) is the reduction of mortality through prompt treatment with effective antimalarials which relies adequately from the support of accurate diagnosis (WHO, 2000).

2.15 Rapid diagnostic tests

Rapid diagnostic tests (RDTs) are immunochromatographic tests that detect parasite-specific antigens in a finger-prick blood sample. Some tests detect only one species (P. falciparum), others detect one or more of the other three species of human malaria parasites (P. vivax, P. malariae and P. ovale) (WHO, 2003). Rapid diagnostic tests are available commercially in different formats, as dipsticks, cassettes or cards. Cassettes and cards are easier to use in difficult conditions outside health facilities. RDTs are simple to perform and interpret, and do not
require electricity or special equipment. WHO recommends that such tests should have a sensitivity of >95% in detecting plasmodia at densities of more than 100 parasites per microlitre of blood. Programme and project managers should make their own choice among the many products available, using the criteria recommended by WHO (www.wpro.who.int/rdt, 2006) as there is as yet no international mechanism for pre-qualification of RDTs.

Current tests are based on the detection of histidine-rich protein 2 (HRP2), which is specific for *P. falciparum*, pan-specific or species-specific parasite lactate dehydrogenase (pLDH), or other pan-specific antigens such as aldolase. These antigens have different characteristics, which may affect suitability for use in different situations and this should be taken into account when developing RDT policy. These tests have many potential advantages, including the ability to provide rapid results, fewer requirements for training and skilled personnel (a general health worker can be trained in one day), reinforcement of patient confidence in the diagnosis and in the health service in general. There are also potential disadvantages, including the likelihood of misinterpreting a positive result as indicating malaria in patients with parasitaemia incidental to another illness, in particular when host immunity is high. The inability in the case of some RDTs, to distinguish new infections from a recently and effectively treated infection is due to the persistence of certain target antigens (e.g. HRP2) in the blood for 1–3 weeks after effective treatment.
The persistence of PfHRP2 in blood for at least one week after treatment can be used in the diagnosis of severe malaria in low transmission areas where artemisinin derivatives are widely available. Patients may have cleared peripheral parasitaemia because of inadequate self treatment, but the PfHRP2 test will be strongly positive, unpredictable sensitivity in the field (WHO, 2004), mainly because test performance is greatly affected by adverse environmental conditions such as high temperature and humidity. Published sensitivities of RDTs for \textit{P. falciparum} range from comparable to those of good field microscopy (>90% at 100–500 parasites/µl of blood) to very poor (40–50%) for some widely used products. Sensitivities are generally lower for other species.

The reasons for poor sensitivity are not clear. They may include poor test manufacture, damage due to exposure to high temperature or humidity, incorrect handling by end-users, possible geographical variation in the test antigen, and poor comparative microscopy (WHO, 2004). Several studies have shown that health workers, volunteers and private sector providers can, with some support and follow-up, learn to use RDTs correctly with relative ease. The use of a confirmatory diagnosis with either microscopy or RDTs is expected to reduce the overuse of antimalarials by ensuring that treatment is targeted on patients with confirmed malaria infections as opposed to treating all patients with fever. There is, however, little documented evidence that this is so.
The main problem is that providers of care, although they may be willing to perform diagnostic tests, do not always comply with the results, especially when they are negative. Being aware that delay in providing effective treatment can be fatal for a malaria patient, they are often reluctant to withhold treatment on the basis of a negative result. WHO is currently supporting operational research projects designed to address these issues (WHO, 2006).

2.16 Immunodiagnostics and PCR-based molecular detection methods

Detection of antibodies to parasites, which may be useful for epidemiological studies, is neither sensitive, specific, nor rapid enough to be of use in the management of patients suspected of having malaria (Voller, 1988). Techniques to detect parasite DNA based on the polymerase chain reaction (PCR) are highly sensitive and very useful for detecting mixed infections, in particular at low parasite densities. They are also useful for studies on drug resistance and other specialized epidemiological investigations (Bates et al., 2004), but are not generally available in malaria endemic areas.

2.17 Individual patient, mothers'/ caretakers’ diagnosis

Patients ordinarily use multiple sources of health care, whose choice is partly determined by the recognition of disease symptoms as well as cost, distance, religious believes and quality of health care (Amuyunzu, 1998; Nyamongo, 2002). Based on previous studies (Alonso et al., 1987; Deressa and Enqeellassie,
where mothers gave accurate diagnosis of their children’s illnesses at home, three hundred and forty nine (349) mothers/caretakers and patients were interviewed using standard closed ended questionnaires to ascertain their ability to diagnose malaria. They were further interviewed to establish their perception of the disease based on signs and symptoms.

Useful epidemiological data based on records of self reported illness or on blood smear examination can be collected at relatively little additional costs. Lack of information relating to self reported cases suggest that a change in approach is required to empower/strengthen mothers/caretakers in diagnosis and home management of malaria when prompt treatment at a health facility is impossible. It is not known whether all cases clinically diagnosed and treated as malaria at the dispensary are accurate. Further more, it is not known whether mothers/caretakers of sick children and individual patients have experience in accurately diagnosing malaria.
CHAPTER THREE  
MATERIALS AND METHODS

3.1 Study area

The study was conducted in Kipsamoite dispensary in Sangalo Location, in Kabiyet Division of Nandi North District, Rift Valley Province in Kenya (Figure 3). The district borders Kakamega District to the North-west, Uasin-Gishu to the North-east, Kericho and Kisumu Districts to the southern and Vihiga District to the West. The district lies within latitudes 0° and 34° North and longitudes 34° 44’’ and 35° 25 East. The altitude of the district ranges from 1,300m to 2,500m above sea level. The district has five administrative divisions: Kabiyet, Kapsabet, Kosirai, Kipkaren, and Kilibwoni. The Kabiyet Division is divided into six administrative locations namely; Sangalo, Kabisaga, Kebolonik, Kabiyet, Kamasai, and Lolkeringet. The Dispensary, a Kenyan Ministry of Health facility, is the only health care facility within an area whose cathment covers approximately 16 square kilometres. Small patches of land have been deforested and planted with crops, and large swamp boarders the eastern parts of the area remain undisturbed. Terrain is hilly and rocky on the western side.
Figure 3: Map of Kabiyet Division showing the study area
The basement rock system gives way to thick red soil. The topography is favourable to the growth of natural forests. The district has a cool and moderately wet climate. On the average, it receives between 1200mm and 2000mm of rainfall per annum in bimodal pattern. The long rain starts from early March to the end of June and the short rains from mid September to the end of November. Most parts experience mean temperatures of 18° C to 22° C and Relative Humidity of over 65%. The rainfall distribution and seasonality to a great extent, influences economic activities undertaken in different parts of the district.

The area experiences unstable, sporadic malaria transmission. A peak in malaria transmission often follows the long rains from March to May, but this peak is sometimes absent or may occur at another time of the year. Mosquito surveys indicate that the predominant indoor resting vector is Anopheles gambiae s.l (97.5%) with occasional Anopheles funestus (2.5%) (Ernst et al., 2006).

3.2 Study population

The ethnic community in the study location is the Nandi. Most of the inhabitants live along Nandi slopes and in hilly areas. The main occupation is farming in cash crops like tea and sugarcane. Food crops grown include maize, beans and vegetables. Cattle’s keeping is also practiced in large scale for both subsistence and commercial purposes. A few houses in the study area are traditionally Nandi type, which consist of round-mud walls and grass thatched roofs. However, most
of the houses in the study area have walls made of mud and roofed with corrugated iron sheets. Due to extended households, families are usually large. The population of Sangalo location is approximately 9,783 (GoK Population census, 2001). A random sample of Kipsamoite residents were surveyed about health seeking behaviour in 2002. Results indicated that the vast majority of residents (80%) sought care at this health facility when they had symptoms of malaria (John et al., 2000).

3.3 Study design

This was based on examination of epidemiological data of the clinical records over a period of seven months of self-reported illnesses by mothers, caregivers of sick children, individuals and microscopic examination of blood smears from patients clinically diagnosed as having malaria infection.

3.4 Inclusion criteria

All consenting patients residing in the catchments area and diagnosed with clinical malaria were recruited in the study.

3.5 Exclusion Criteria

Those clients not consenting and/or diagnosed with ailments other than malaria were excluded.
3.6 Sample size determination

The sample size was determined using the formula as designed by (WHO, 2001) where;

\[ n = Z^2 (p)(100-p) \times \text{DEFF}/d^2 \]

Where

- \( n \) = Sample size
- \( Z \) = standard normal deviate (1.96) which corresponds to 95% confidence interval.
- \( p \) = Proportion of target population estimated to have particular characteristics.
- \( d \) = Acceptable difference of estimate from the true value
- \( \text{DEFF} \) = Design effect = 1

The prevalence of malaria in the general population in Kenya highlands ranges from 35-50% (John et al., 2000), 38% (Nandi District Development plan of 2002-2008). In this study, a prevalence of 35 % was assumed. Thus \( N=1.96^2 \times (65) \times (35) \times 1/5^2 = 349 \), therefore a sample size of 349 was sampled.

3.7 Sampling procedures

Any patient who was referred by the clinical officer or nurse to the laboratory by the clinical officer/nurse after presumptive diagnosis of malaria and fulfilling the inclusion criteria was enrolled in to the study. A total of three hundred and forty nine patients attending the clinic were recruited.
3.8 Clinical diagnosis of malaria

Clinical officer or nurse took demographic details and ailment history for all patients reporting to the dispensary. The patients were also categorized by age group (under 5 and above 5) according to the Kenya National Malaria prevention, control and treatment guideline for health workers (MoH, 2006). Clinical examination was done on each patient, including taking of auxiliary temperatures followed by presumptive diagnosis for clinical malaria. Malaria case was defined as clinical episode of illness in a person with fever or recent history of fever with/without other signs and/or symptoms of malaria (WHO, 2006). All cases diagnosed as clinical malaria were referred to the laboratory for microscopic malaria examination tests.

3.9 Parasitological diagnosis of malaria

Patients testing positive for clinical malaria and referred for blood smear (B/S) for malaria parasite test, had a finger prick and both thick and thin blood films were prepared on pre-labelled clean slides for identification of malaria parasites. Thin films were fixed with methanol to preserve red cell morphology and both smears stained with 3% Giemsa solution for 1 hour. The slides were then air dried and examined under compound light microscope using x 100 objective. Malaria infection in patients was defined as those who had parasitological confirmed results (WHO, 2005). Parasites, if any, were counted against leucocytes in each microscopic field until 200 leucocytes were counted. Thick films were used for
rapid parasite identification and counts while thin films were examined for speciation. A slide was considered negative after 100 microscopic fields were examined without identifying any *Plasmodium* parasites.

### 3.10 Individual patient, mothers’/ caretakers’ diagnosis

Questionnaires were developed and pilot tested within the study area before use. Three hundred and forty nine (349) mothers/caretakers and patients were interviewed using closed ended questionnaires (Appendix ) to ascertain their ability to diagnose malaria. They were further interviewed so as to establish their perception of the disease based on signs and symptoms.

### 3.11 Ethical consideration and clearance

Informed consent was obtained from individual patients, mothers/caretakers of the sick children. Confidentiality of the patients was assured and maintained throughout the study. All cases that required treatment were treated appropriately. The study was reviewed and approved by the Ministry of Education, Science and Technology and Ministry of Health upon recommendation from Kenyatta University. Kipsamoite Community was informed before the research commenced and consent gained.
3.12 Data management and analysis

The data gathered from both laboratory and closed ended questionnaires were edited and stored in book-form as an Ms excel spreadsheet. Data were backed-up using floppy and computer disks. The data was cleaned for errors and outliers. All data analyses were done in SPSS.
CHAPTER FOUR

RESULTS

4.1 Prevalence of malaria in patients attending Kipsamoite dispensary

A total of 349 patients were diagnosed for malaria in Kipsamoite dispensary during the period of the study. The overall prevalence rate of malaria infection reported based on microscopic diagnosis was shown be 113/349 representing 32.4% while the prevalence by mothers/ guardians/ individuals’ diagnosis was reported to be 214 representing 61.3%. The diagnosis by clinical officer or nurse classified all the 349 patients as having malaria showing a prevalence of 100%. Out of the 214 patients diagnosed by mothers/ guardians/ individuals’, 113/214 representing 52.8% were confirmed by microscope as true positives and 101/214 representing 47.1% as false positives. Similarly, of the 349 diagnosed by clinical officer/ nurse as positive for malaria, 113/349 representing 32.4% were confirmed as true positives and 67.6% as false positive. The mothers/guardians/ individuals’ diagnosis reported less false positives compared to clinical officer/nurse diagnosis. (Figure 4).
4.2 Variation of malarial infection by age groups

All the 349 patients gave their actual ages. In the age group < 5 years 27/109 (24.8%) were infected with malaria while 82/109 (75.2%) were negative for malaria by microscopy. In the age group > 5 years 86/240 (35.8%) were infected with malaria while 154/240 (64.2%) were negative (Table 1). The infection distribution was significantly associated with age groups < 0.05 ($\chi^2 = 4.190$).
Table 1: Distribution of malaria infection by age groups

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Microscopy results</th>
<th>Prevalence (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>27</td>
<td>82</td>
<td>24.7</td>
</tr>
<tr>
<td>&gt;5</td>
<td>86</td>
<td>154</td>
<td>38.5</td>
</tr>
<tr>
<td>Total</td>
<td>113</td>
<td>236</td>
<td>32.4</td>
</tr>
</tbody>
</table>

4.3 Distribution of malaria infection within residential areas

Distribution of malaria infection among patients analyzed according to residential areas showed slight variation. The village located in proximity to Chepyewet showed malaria infection in 32/79 representing 41% prevalence. The population living at the eastern hill slopes of Kipsagat showed malaria infection in 10/23 representing 43%. The Eastern forest village of Moraongen showed malaria infection in 21/81 representing 26% while the Northern hill slopes of Kipsamoite had 10/31 representing 32.2% of malaria infections. The villages within the area of the valley of Kwidich and Kapkweino showed malaria infection of 10/44 representing 23% while the village situated in the lower land plains of Kapkuto showed malaria infection of 15/59 representing 25% of the cases and the village situated towards the western forest area of Kamwega showed malaria infection of 17/32 representing 53% (Figure 5). The results showed that the distribution of malaria infection was not dependent on residential villages. Overall, there was no
significant difference in the distribution of malaria infection among these seven residential areas.

![Figure 5: Distribution of malaria infection within residential areas](image)

**Figure 5: Distribution of malaria infection within residential areas**

### 4.4 Body temperature as an indication of malaria infection

Microscopy analysis it was showed that patients with body temperatures ranging from 34°C–34.9°C, had no infection reported. Patients with body temperatures ranging from 35°C–40°C were infected with malaria. The prevalence of malaria infection ranged from 12.5% at 35°C to 63.5% at 40°C. Body temperature range was analyzed by cross tabulation (Pearson $\chi^2$). The results showed a significant association between body temperature range groups and malaria prevalence.
P<0.001 ($\chi^2=47.283$). There was a tendency of high malaria prevalence in high body temperatures range groups. The higher the body temperature the more likely an individual tested positive for malarial infection (Table 2).

**Table 2: Body temperature and association with malarial infection**

<table>
<thead>
<tr>
<th>Body temperature range ($^{\circ}C$)</th>
<th>Microscopy results</th>
<th>Total</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>34-34.9</td>
<td>5</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>35-35.9</td>
<td>21</td>
<td>3</td>
<td>24</td>
</tr>
<tr>
<td>36-36.9</td>
<td>90</td>
<td>27</td>
<td>117</td>
</tr>
<tr>
<td>37-37.9</td>
<td>64</td>
<td>20</td>
<td>84</td>
</tr>
<tr>
<td>38-38.9</td>
<td>36</td>
<td>21</td>
<td>57</td>
</tr>
<tr>
<td>39-39.9</td>
<td>16</td>
<td>35</td>
<td>51</td>
</tr>
<tr>
<td>40-40.9</td>
<td>4</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>236</strong></td>
<td><strong>113</strong></td>
<td><strong>349</strong></td>
</tr>
</tbody>
</table>

**4.5 Variation of parasitaemia with malaria infection**

The malarial parasite density was zero for the 236 patients representing 67.6% of those who tested negative for malarial infection using microscopic diagnosis. Those patients with detectable malarial infection had the following ranges of parasitaemia: 24 patients representing 16.9% had < 100/ 200 WBC parasitaemia, 14 patients representing 4% had 101-200/ 200 WBC, 9 patients representing 2.6%
had 201-300/200 WBC, 6 patients representing 1.7% had 301-400/200 WBC. Furthermore, 6 patients representing 1.7% had 401-500/200 WBC, 7 patients representing 2% had 501-600/200 WBC, 9 (2.6%) had 701-800/200 WBC, another 7 representing (2%) had 801-900/200 WBC and 30 representing (8.6%) had >900/200 WBC. Significantly many patients had parasite densities of > 900/200 WBC. P = 0.0001 ($\chi^2 = 349$, df = 102). Parasitaemia distribution was independent of the location of the patients (Table 3).

**Table 3: Parasitaemia in relation to residential area**

<table>
<thead>
<tr>
<th>Residential area</th>
<th>Minimum parasite density</th>
<th>Maximum parasite density</th>
</tr>
</thead>
<tbody>
<tr>
<td>Near swamp area</td>
<td>2.8</td>
<td>5.7</td>
</tr>
<tr>
<td>Eastern hill slope</td>
<td>3.2</td>
<td>4.9</td>
</tr>
<tr>
<td>Eastern forest area</td>
<td>2.2</td>
<td>5.4</td>
</tr>
<tr>
<td>Valley area</td>
<td>2.5</td>
<td>5.2</td>
</tr>
<tr>
<td>Lower land plains</td>
<td>2.6</td>
<td>4.9</td>
</tr>
<tr>
<td>Northern hill slopes</td>
<td>2.8</td>
<td>4.8</td>
</tr>
<tr>
<td>Western forest area</td>
<td>2.7</td>
<td>4.5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2.2</strong></td>
<td><strong>5.7</strong></td>
</tr>
</tbody>
</table>
Parasite density distribution based on analysis by one way analysis of variance (ANOVA) revealed that there was no significant difference in mean parasite density distribution over the seven residential area categories $P = 0.261$ ($F = 1.305$).

4.6 Correlation between parasite density and body temperature

Based on microscopic results, the linear association (correlation) between body temperature, and the malarial parasite density among the 113 patients (32.4%) with confirmed malarial infection revealed no significant relationship between body temperature and malaria parasite density $P=0.113$ ($t =1.597$) (Figure 6).
Figure 6: Correlation between body temperatures with parasite density

\[ \text{Body temperature in degrees celcius} \]

\[ \text{Log10 parasite density} \]

\[ \text{Rsq} = 0.0224 \]
CHAPTER FIVE

DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS

5.1 Discussion

The study aimed at evaluating the accuracy of clinical, mothers’/caregivers’ and self diagnosis by patients using microscopy as the gold standard with a view to determine their strengths in malaria diagnosis or further emphasis for laboratory support to malaria disease management. Microscopy has been used to detect malaria parasites in the blood of infected patients since Laveran first identified the parasites (Laveran, 1880).

Using microscopy as the gold standard, the present study showed that overall malaria prevalence among the population was 113 (32.4%). This was considerably low compared to other studies by Munyekena et al., (2005) who reported a prevalence of 62.8% in Iguhu village Kakamega district, 72% in the general population in Uasin Gishu, Kenya (Some, 1994) and 39.2% in the general population Kericho district (Ayisi et al., 1992). It cannot however, be conclusively stated that the prevalence of malaria in this area was low compared to other regions in Kenya. It is recognized that malaria distribution is influenced by seasons for example, Shilielu et al., (1998) reported prevalence rates at 44% in the dry seasons and 55.4% in the wet season in Mumias, Kenya. Similarly land topology and geographical zones influence malaria distribution. Spencer et al.,
(1987) and Githeko et al., (1993) observed that the prevalence of *P. falciparum* malaria in school children in the low-altitude region of Lake Victoria basin (elevation ≈ 1, 200 m) adjacent to the highlands reaches >80%, which was much higher than malaria prevalence in highlands.

Age as an influencing factor in malaria infection was also evaluated during this study. Malarial infection ranged from 0 % to 35.8 % among those aged > 5 years and 0 to 24.7 % among those aged < 5 years. The infection distribution was significantly associated with age groups. This finding is a departure from observations by Svenson et al., (1995), who found that severity of malaria was not age dependent. However, other studies have noted higher prevalence of malarial infection among children aged 1-4 years (Munyekenye et al., 2005). The lower prevalence of malaria infection among children less than 5 years of age reported in this study could have been attributed to preference by parents and caregivers to protect their children with insecticide treated bed nets which had been introduced by the Government of Kenya (MoH, 2001). Lack of adequate protective measures such as long lasting insecticide treated nets (LLINs) among the group aged above five years could have been a contributing factor for the higher rate of infection observed among this group.

In Kapsamoite, older age had been associated with reduced risk for malarial infection (Ernst et al., 2006). Schwart et al., (2001) observed a positive
association of malaria severity and age. Baird et al., (1998) observed mortality from malaria to be highest in the youngest (< 2 years) and oldest age groups (> 40 years), 2.2 % and 2.5 %, respectively, compared with 0 % – 0.9 % for patients who were 2 – 40 years of age. Conversely, the possible explanation for the high prevalence of malaria infections reported in this study for adults suggests that these persons being from the highlands are likely to have passive or no immunity to malaria.

Malaria prevalence was also observed to vary according to residential areas. The prevalence ranged from 23 % in Kapkweino/Kwindich, located in the valley area to 53 % in Kamwega situated to the western forest area. Other studies have shown that such variations could be due to housing characteristics among other factors (Guthman et al., 2001). Ernest et al., (2006) observed in the same area that nearness to swamp and forest are risk factors for malaria infection. This concurs with the current study findings which indicate that both residential areas (Chepyewet, located near swamp and Kamwega, situated near the forest) as having higher prevalence rates of infection as compared to the rest of the villages.

The prevalence of malaria in the highlands of Eastern Africa has been shown to vary spatially and temporally as a result of seasonal variation and topography (Balls et al., 2004). The topography of the highlands comprises hills, valleys and plateaus. Rivers and streams flow along the valley bottoms in the valley ecosystem and swamps are a common feature. Unlike in lowland plains, where
drainage is poor and mosquito breeding habitats have an extensive distribution, the majority of breeding habitats in the hilly highlands are confined to the valley bottoms because the hillside gradients provide efficient drainage (Minakawa et al., 2004). The non-homogeneous distribution of larval breeding habitats is likely to affect adult vector spatial distribution and may, consequently, lead to focal malaria transmission and heterogeneous human exposure to malaria.

The malaria immunity profile in the highlands is likely to be influenced not only by age, but also by distance from the foci of transmission. Other studies have also reported similar findings (Githeko et al., 2006; Marsh, 1992). The pattern of malaria transmission in the highland plateau ecosystems may be less distinct due to the flat topography and the more diffuse hydrology resulting from numerous streams. The distribution of malaria infection within this study area was however not dependent on residential villages.

This study observed association between patients’ body temperature and malaria infection. It was indicated that the higher the body temperature the more likely an individual tested positive for malarial infection. Body temperature was also associated with patient’s age. Similar results have been reported by Legros et al., (2007) who observed fever (elevated temperatures) as the most common initial symptom for the patients who had severe malaria and or death due to malaria in
France. Bloland et al., (1999) also observed elevated temperatures among children aged 6–11 years who also had high malarial prevalence.

Parasitaemia loads were associated with body temperatures ranging between 35 °C - 40°C ($P = 0.0001$). These observations equate other studies by Delley et al., (2000), who reported higher parasite counts among human subjects who had a temperature above 35 °C. Other studies have provided evidence for an age-dependent threshold effect of parasitemia on the occurrence of fever (Rogier, et al., 1996). The level of such thresholds varied by 2.45 trophozoites per leucocyte, maximum at one year of age, to 0.5 trophozoites per leucocyte, minimum at 60 years of age (Rogier, et al., 1996). As immunity develops, the number of parasites an organism can tolerate before developing fever increases (Smith et al., 1994b). Density thresholds have been proposed for the development of fever in response to malaria infection, for example, a threshold of 500 parasites/mm$^3$ for adults was proposed (Vellema et al., 1991). On the other hand, studies have shown that thresholds vary depending on study population, endemic zone, season, adults and children from 500 to 15,000 parasites/mm$^3$ (Boudon et al., 1986).

The current study reported the ability of clinical and mothers/guardians’/individuals’ to diagnose malaria as 32.4 % and 52.2 % respectively. This suggests that mother/guardian diagnosis is closely proximate to microscopic diagnosis compared to clinical diagnosis. These finding concur with
other observations that have recognized clinical diagnosis alone reporting a very low accuracy (Zorovac et al., 2008).

The parent, guardian or self diagnosis of malaria infection is often the first and probably the only main diagnostic approach used in rural areas, with limited resources in Kenya. Prompt and accurate diagnosis of malaria is part of effective disease management and if implemented effectively, could help to reduce unnecessary use of antimalarials. High sensitivity of malaria diagnosis is important in all settings, in particular for the most vulnerable population groups, such as young children, in which the disease can be rapidly fatal. High specificity can reduce unnecessary treatment with antimalarials and improve differential diagnosis of febrile illness. The second clinical diagnosis is often sought after the self diagnosis and medication has failed (Nyamongo, 2002). The diagnosis of malaria is based on clinical diagnosis supplemented by the detection of parasites in the blood (WHO, 2006). In areas where parasitological diagnosis is not currently available, the decision to provide antimalarial treatment in these settings must be based on the prior probability of the illness being malaria. Clinicians need to weigh the risk of withholding antimalarial treatment from a patient with malaria against the risk associated with antimalarial treatment when given to a patient who does not have malaria. However, concerns have been raised over its specificity in diagnosis of malaria. The findings of this study will go a long way to improve on the strategies of malaria control especially through prompt and
effective treatment of malaria cases as stated in the roll back malaria targets in the Abuja declaration of the year 2000.

5.2 Conclusions

i. Mothers’/caregivers’ of sick children and individuals’ diagnosis of malaria were more proximate to microscopy compared to the clinical officer’s/nurse’s.

ii. There was significant correlation between malaria infection and age of patients attending Kipsamoite dispensary. The patients aged 5 years and above were more infected with malaria than those aged less than five years.

iii. The prevalence of malaria infection among the study population was 32.4% with no significant variation between the residential areas. There is therefore no need for prioritization of control interventions to any particular residential area.
5.3 Recommendations

i. There is need to train and encourage mothers/caregivers and individuals to be able to recognize the signs and symptoms of malaria with a view to improving management of uncomplicated malaria at home.

ii. There is need for refresher training of the clinical officer/nurse on malaria case management to improve their knowledge and skills in clinical diagnosis of malaria.

iii. There is need to support the diagnosis by clinical officer/nurse with parasitological confirmation (Microscopy or Rapid Diagnostic Tests) to minimize irrational use of antimalarial medicines.

iv. Patients above five years of age should be targeted and encouraged to access malaria control interventions especially the use of insecticide treated bed nets.
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APPENDIX

QUESTIONNAIRE

EVALUATION OF MALARIA INFECTION IN RELATION TO AGE, RESIDENCE AND DIAGNOSIS OF PATIENTS ATTENDING KIPSAMOITE DISPENSARY, NORTH NANDI DISTRICT, KENYA.

Questionnaire for individuals/ mothers/ caretakers’ malaria diagnosis.

Part A: Individual malaria

Q1)(a) Your name_________________________________
(b) Your village_________________________________
(c) Age/ year of birth____________________________
(d) Auxiliary temperature (0°C)_____________________

Q2) How do you feel when you have malaria? Prompt. Anything else? If participant does not mention symptoms Mark 0 = not present in adjacent to numbered box, otherwise tick for each response.

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>1</td>
<td>Fever/ chills/ sweating.</td>
</tr>
<tr>
<td>2</td>
<td>Headache</td>
</tr>
<tr>
<td>3</td>
<td>Body ache/ Joint pains</td>
</tr>
<tr>
<td>4</td>
<td>Vomiting/ nausea</td>
</tr>
<tr>
<td>5</td>
<td>Weakness/ lethargy</td>
</tr>
<tr>
<td>6</td>
<td>Gas/ diarrhea/ stomach ache</td>
</tr>
<tr>
<td>7</td>
<td>Other(s) ____________________________________________</td>
</tr>
</tbody>
</table>
Q3) which disease do you think you are suffering from now, which has made you seek treatment

Part B: (Child’s malaria)

Q1)(a) Child’s name
(b) Village name
(c) Age/ year of birth
(d) Auxiliary temperature (0°C)

Q2) which of the following symptoms/ signs would suggest malaria in a child. Prompt. Anything else? If participant does not mention symptoms mark 0 = not present in adjacent to numbered box, otherwise tick for each response

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fever/ chills/ sweating.</td>
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<td>Body ache/ Joint pains</td>
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<td>4</td>
<td>Vomiting/ nausea</td>
</tr>
<tr>
<td>5</td>
<td>Weakness/ lethargy</td>
</tr>
<tr>
<td>6</td>
<td>Gas/ diarrhoea/ stomach ache</td>
</tr>
<tr>
<td>7</td>
<td>Other(s)</td>
</tr>
</tbody>
</table>
Q3) which disease do you think the child is suffering from now, which has made you seek for treatment? _________________________________