Antimalarial Prescription Practices for Children with Negative Microscopy Results for Malaria Parasites admitted at the Moi Teaching and Referral Hospital, Kenya

By

Simba, Justus Maingi MBChB (Moi)

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Declaration

I declare that this thesis is my original work and that it has not been presented elsewhere for any academic purpose in any institution of higher learning. No part of this thesis can be reproduced without prior permission from the author and/or Moi University.

Simba, Justus Maingi: Signature …….. Date ……

SM/PGCHP/02/11

This thesis has been presented with our approval as university supervisors;

Prof. S. O. Ayaya: Signature ……Date ……...

Department of Child Health and Paediatrics

Dr. I. K. Marete: Signature ……..Date ……..

Department of Child Health and Paediatrics

Dedication

Dedicated to the patients who may have passed on since we really never knew what caused their fever, for it is now more apparent that we may have over diagnosed malaria and suffered the ultimate consequences.

Abstract

Background: The burden of malaria is declining globally including Kenya, however a high number of patients continue to be treated for malaria in our set up. Malaria parasite resistance, especially of *Plasmodium falciparum,* to artemisinin drugs can reverse these gains. This scenario can be prevented by adopting correct diagnosis and appropriate treatment. Adherence to test results is cost effective, prevents resistance and has been shown to save lives. The study sought to evaluate clinicians' adherence to negative malaria test results in a referral hospital.

Objective: To determine the clinicians' antimalarial prescription practices in the management of children with negative microscopy results.

Methodology: A prospective observational study was carried out on children, aged 1 month to 14 years, admitted with a negative microscopy results for malaria parasites at the general paediatric wards of Moi Teaching and Referral Hospital, Kenya. Data was collected from December 2012 to June 2013 using a structured questionnaire. The primary outcome was antimalarial prescription, while secondary outcomes were: antibiotic use, duration of stay in hospital, discharge home, or death. Data was analysed using STATA version 10 software at 95% level of confidence. Descriptive statistics were generated for continuous and categorical data. Chi-square test, Kruskal-Wallis test and logistical regression were used to test for associations among variables.

Results: A total of 250 participants were enrolled. The median age was 19.5 months (IQR10, 36) with 150 (60%) being male. Forty one (16%) of the participants had travelled to malaria endemic regions in the preceding 4 weeks while 30 (12%) had used antimalarial prior to admission. Those treated with antimalarial with negative microscopy results were 34 (13.6%). History of travel, increased sleepiness, convulsions, headache, having been on antimalarial prior to presenting to hospital, pallor and abnormal central nervous examination findings were associated with antimalarial prescription despite negative test results. Presence of cough was associated with reduced likelihood of treatment (P value <0.05). Increased sleepiness, history of headache and prior antimalarial use were independent clinical characteristics associated with treatment. Antibiotics were concurrently used with antimalarial in 30 (88.2%) of the patients with odds ratio of 1.212 (95%CI 0.40-3.68). The mean duration of hospital stay was 3.53 days for those on anti-malarial versus 3.75 days for those not treated which was not statistically different(P =0.61). One participant died in the group not on antimalarial.

Conclusion: There was a substantial proportion (13.6%) of children treated for malaria with negative microscopy results. Increased sleepiness, headache and having been on antimalarial prior to hospitalization, influenced the treatment. No differences were noted in duration of hospital stay, antibiotics prescription, discharge home or death in comparison with the group not treated. A similar study in the outpatient set up is recommended.

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List of Abbreviations:

ACT -Artemisinin-based combination therapy

AL -Artemether Lumefantrine

AVPU Scale- **A**lert, response to **V**erbal, **P**ain and **U**nresponsive scale

BS for MPs- Blood Slide for Malaria Parasites

CNS- Central Nervous System

ENT- Ear, Nose and Throat

HIV -Human Immunodeficiency Virus

Hx- History

IMCI-Integrated Management of Childhood Illnesses

IREC- Institutional Research and Ethics Committee

MTRH -Moi Teaching & Referral Hospital

PCR- Polymerase Chain Reaction

PI- Principal Investigator

RDTs -Rapid Diagnostic Tests

RS- Respiratory system

Rx- Treatment

WHO -World Health Organization

Operational Definitions:

1. Negative blood slide: This is a smear which plasmodium parasites have not been seen by the laboratory personnel and thus reported as negative.
2. Acute illness: A disease which is characterized by a single or repeated episode of relatively rapid onset and short duration in our case of less than 14 days.
3. Treatment with antimalarial: Being on antimalarial 24 hours after admission while the microscopy result was negative for malaria parasites.
4. Outcomes: This referred to the hospital outcomes of death in the ward or discharge of a patient from the ward with the associated duration to either. It also referred to treatment based outcomes of being on antimalarial.

CHAPTER 1: INTRODUCTION

1.1 Background Information:

Malaria remains an important cause of morbidity and mortality in the world. In 2012 there were estimated 207 Million people affected by malaria worldwide with 627,000 deaths. Kenya had 9 Million suspected cases reported but only 1.4 Million were confirmed with diagnostic tests. Seventeen percent of them were aged less than 5 years of age (1).

The diagnosis of malaria nowadays requires confirmation with a blood slide for malaria parasites. Previously, the diagnosis advocated mainly by *integrated management of childhood illnesses* (IMCI) guidelines put a lot of emphasis on presence of fever especially in those children aged less than 5 years. Fever in itself could be caused by several conditions including pneumonia, otitis media, pharyngitis, urinary tract infection and human immunodeficiency virus (HIV) infection. This meant even what may not have been malaria may have been treated as malaria (2). This has since changed. The current guidelines both by World Health Organization (WHO) and the Kenyan Ministry of Health require parasitological diagnosis for all patients irrespective of age unless it is not available (3,4).

The shift in policy guidelines has been informed by evidence which indicates overreliance on clinical diagnosis of malaria has many problems including likelihood of increased drug resistance, misdiagnosis and wastage of health resources thus increasing cost of health services (5,6,7,8).

The percentage of patients having a parasitological test improved from 37% in 2010 to 61% in 2012. However, millions of people suspected to have malaria still did not receive a diagnostic test, this despite WHO having recommended tests for all people, irrespective of age, before starting them on antimalarial (1). Further though the blood slides for malaria parasites are requested in Africa, many clinicians do not seem to use them. Many excuses have been given including unreliable laboratory results (9).

Moi Teaching and Referral Hospital (MTRH) being a tertiary institution is expected to be at the forefront in adhering to these policy guidelines since availability of diagnostic tools is not a problem as may occur with level 2 and 3facilities in the community. Further, the validity of routine blood slide for Malaria parasites at this hospital was recently shown to be high, which is, sensitivity of 75% and specificity of 84.8% when compared to polymerase chain reaction (PCR) (10). However hospital data revealed that most patients started on antimalarial had blood slides negative for malaria parasites. More than a third of all the patients in the paediatric wards have a blood slide done for malaria parasites (10). Adherence to this policy at such a level is likely to prevent the problems associated with over diagnosis of malaria and decrease the burden on resources. Moreover being a teaching hospital, the culture imparted to both undergraduates and postgraduate students, is key in ensuring that Kenya adheres to this policy.

This study evaluated whether clinicians in a national referral hospital adhered to test results when making a diagnosis of malaria in children in an inpatient set up. In the wards the clinicians have the results available to them and thus in a position to stop antimalarial if not indicated thereby saving on the cost of antimalarial being used when not required. The

focus of many studies in the region has been outpatient and thus this study shows inpatient practices. By providing information on whether there is any logical basis in terms of treated and not treated patients where blood slide was negative for malaria parasites, the study provides information on the utilization of blood slide results in malaria diagnosis and treatment and the reasons thereof.

The information gathered becomes an eye opener to the current practice at such an institution and its implication on adherence to test results by clinicians

1.2 Problem Statement:

Moi Teaching and Referral Hospital's catchment area is a low malaria endemic region (4). A review of patients' files showed that up to 15% of children are treated for malaria at MTRH. On the other hand only 13% of patients treated for malaria had a blood slide positive for malaria in 2010 with some having unknown test results (10). It was not clear which patients who were negative for malaria parasites were put on antimalarial.

Indiscriminate treatment with antimalarial is likely to lead to unnecessary morbidity and mortality as other illnesses are likely to be missed. In a prospective study done in Tanzania, mortality in test negative results patients treated for malaria was significantly higher at 12.1% compared to 6.9% in test positive group (11). It may contribute to drug resistance and wastage of resources (6,12). On the other hand, Njama-Meya D. et.al in 2007 in a prospective study in Uganda showed that only 0.8% of patients with malaria were likely to be missed if treatment of malaria was restricted to laboratory-confirmed cases only (13).

Studies have shown that although it is thought that malaria is diagnosed clinically due to lack of diagnostic tests in Africa, this is not correct as their availability has not been shown to affect diagnosis as shown by Barat et.al in Zambia (14) and Marete et.al at MTRH (15). MTRH being a referral hospital has capacity to diagnose malaria, other reasons may therefore be behind the treatment of malaria in test negative results.

In outpatient set ups, it has been shown that clinicians ignore the negative test results but not the positive as most studies show that there is above 95% treatment for those with positive slides. The problem of unreliability seems not to occur in this case (9,16,17).

CHAPTER 2: LITERATURE REVIEW

2.1 Epidemiology of Malaria

Malaria is a febrile illness caused by Plasmodium parasite. The species which commonly infect humans include the *P. falciparum, P. ovale, P. malariae* and *P. vivax*. *Plasmodium knowlesi* which usually infects primates has also been shown to infect humans recently. *Plasmodium falciparum* is the most spread and is the one responsible for most severe forms of malaria. It is transmitted by a bite of an infected female anopheles mosquito (18).

Malaria occurs worldwide though more concentrated in the tropics. The numbers of cases of malaria are estimated to have decreased globally from 244 million in 2005 to 207 million in 2012, with the number of deaths decreasing in the same period from 985,000 to 627,000. Malaria mortality rates have fallen by more than 45% globally since 2000, and by 49% in the WHO African Region. In children this reduction in mortality was even more at 54% in the African region. The same report showed there was evidence that the burden of malaria is reducing in Africa including Kenya, though with limited data for the latter and is mainly associated with effectiveness of control measures. The number of fevers also attributable to malaria has been decreasing. However, 90 percent of these deaths occur in Africa where 1 in every 5 child deaths (18%) is due to malaria. In Kenya 13% of 'under 5 mortality' is due to malaria. It is estimated that 23% of under 5 year old presenting to health facilities in Kenya with fever receive antimalarial (1,19,20,21,22).

In Kenya malaria transmission rates vary from one area to the other with areas around the large water bodies having the highest and the cooler areas experiencing the least. Nearly half, (49%), of Kenyan population lie in high transmission areas though concentrated in a

small area of Kenya. The areas in former Western province are high Malaria regions together with the former Nyanza Province, areas of Rift Valley around Moi Teaching and Referral Hospital lie under low transmission regions of the country with epidemics likely to occur when temperatures are favourable above 18^{o}C (4).

2.2 Presentation of Malaria:

2.2.1 Clinical Presentation:

Symptoms appear seven days or more (usually 10–15 days) after the infective mosquito bite. These usually include: fever, headache, chills and vomiting, which may be mild and difficult to recognize as malaria especially in infants who may just have restlessness, drowsiness, listlessness or refusal to feed. *P. falciparum* malaria can progress to severe illness often leading to death within 24 hours if not treated. In children malaria may present as a syndrome such as severe anaemia, respiratory distress or as cerebral malaria. Signs of cerebral malaria include fever, impaired or loss of consciousness, and convulsions with normal cerebral-spinal findings. Other presentations of severe illness include jaundice, circulatory collapse and abnormal bleeding (4,18).

2.2.2 Laboratory Features:

While specific features on laboratory are only related to presence of plasmodium parasites as described in the parasitological diagnosis below, other laboratory features can be noted. These laboratory features are usually not specific although certain changes in the full haemogram have been noted in children with malaria. These changes include decrease in the haemoglobin level, haematocrit, total white blood cell count, neutrophils and platelets while lymphocyte and monocytes are usually increased (23). Human immunodeficiency

virus (HIV) has been shown to worsen the decrease in haematological parameters especially so for platelets (24).

2.3 Diagnosis of Malaria:

The diagnosis of malaria can be made either clinically or parasitological using microscopy or rapid diagnostic tests (RDTs).

2.3.1 Clinical Diagnosis:

The clinical diagnosis of malaria seems to be employed in many clinical set ups. Fever in many areas is normally treated as malaria (2). Notably though fever can be caused by many other conditions like otitis media, urinary tract infections, and pneumonia, and thus overdependence in it lead to over diagnosis (25). HIV infection worsens this making it harder to diagnose malaria with fever alone as it can result from a wider range of conditions. The relationship however between malaria and HIV is not clear in children as it is in adults (26).

There has however been no consensus on what parameters predict malaria clinically. In several studies some of the parameters thought to predict malaria include fever, shivering, reduced feeding, and abnormal sleepiness, absence of a cough, splenomegaly, hepatomegaly, anaemia, thrombocytopenia and hypoglycaemia (27,28,29,30). Bojang et.al in a prospective study to evaluate a clinical algorithm developed by Olaleye et.al in 1998 observed that the clinical features used could help in predicting malaria in endemic region by around 88% in Gambian children (27,31). However this was shown not to be sufficient in diagnosing malaria (32). Similar findings of lack of utility of algorithms were shown by Mwangi et.al in a study in Kilifi, Kenya (33). On the other hand, although clinical

diagnosis has sensitivity as high as 100%, its specificity is as low as 0-9% (6). Clinical diagnosis of malaria is associated with unnecessary use of antimalarial, unnecessary mortality due to not treating correct cause of illness (5,6,7,8).

2.3.2 Parasitological Diagnosis:

In view of the problems associated with clinical diagnosis of malaria and lack of consensus on what really is malaria, the WHO and subsequently the Kenyan government changed the policy of diagnosing malaria in children. For nearly twenty years, until 2009, the policy had been that children under five years should be diagnosed to have malaria if they have fever, but currently a parasitological test is necessary to put a child on antimalarial. The current IMCI which is supposed to be used in lower health facilities to enable staff with minimum knowledge save children has also included test of malaria to make the diagnosis (3,34).

The WHO, advocates for microscopy or RDTs for making a parasitological diagnosis in clinical practice. Polymerase chain reaction and serological tests are not recommended for clinical diagnosis. While RDTs do not require a lot of technical knowhow, they remain positive for up to three weeks after treatment and may not be economical where large scale testing is done (3).

Microscopy of thick blood films is the usual diagnostic test for *Plasmodium falciparum* malaria. Density is usually assessed by thick films, either by counting parasites per microscope field, or by counting parasites per hundred white blood cells. Thick films contain several layers of red cells, whereas thin films contain a single layer of spread red cells. Thus, for a fixed number of microscope fields, thick films allow the microscopist to

examine a larger number of red cells for the presence of parasites, and low parasitemia can be more readily identified by thick film. Thin films are preferred to examine the morphology of parasites and determine species. Normally two types of stains are used in preparation of these films; these are either Field stain or Giemsa staining. The Kenyan ministry of health advocate for Giemsa staining, although freshly prepared Field stain can also be used (3,4).

Microscopic diagnosis has many advantages, for example, it: has low direct costs if the infrastructure to maintain the service is already available; is sensitive if the quality of microscopy is high; can differentiate between malaria species; can determine parasite densities and can also be used to diagnose other diseases . On the other hand, there are limitations to it especially at the peripheral facilities where quality may not be assured with increased work load and lack of supervision. The microscopes have to be maintained in good order for one to get reliable results (35).

The sensitivity of microscopy is high (≥90%) though may become lower in field conditions (3). Although data is not available on the effect the guideline to diagnose malaria with parasitological test will have, available data show that diagnosis of malaria even where microscopy is available may not always follow this. Overall the percentage of reported suspected malaria cases receiving a parasitological test has increased between 2010 and 2012, particularly in the African region, that is, from 37% to 61%. In Kenya, out of 9 million cases of suspected malaria, only 1.4 million cases were confirmed despite close to 6 million patients having received antimalarial in 2012 (1). This may however not be a reflection of unavailability of diagnostic tests as a study done by Barat, in Zambia showed

antimalarial were prescribed with equal frequency to those who were referred (56%) and those not referred (58%) for a blood slide (14). Zurovac et.al in a study involving two districts in Kenya in 2006 showed that 79% of patients with negative blood slides received antimalarial (17). Recently, in a study involving the whole country, Juma and Zurovac showed a lower percentage of 56.6% and 50.4% of those below and above 5years respectively, received an antimalarial when a test was negative for malaria (16). Similarly, Reyburn at varied periods, in different regions in Tanzania showed varied proportions of the patients treated for malaria while negative with the least being 48% (36,37).

While there have been many studies showing that clinicians may not trust microscopy results from the lab, for example Derua et.al, showed a reliability of 41%, there is no significantly increased trust for RDTs which do not really depend on the capability of the technician as shown by Chinkhumba et.al (9,38).Notable on the other hand, close to 100% of patients with positive slides are always put on antimalarial (5,39,40).This shows that it may just depend on the willingness of the clinicians to adhere to the tests they order. Ngasala et.al in a rural based study in Tanzania showed there was improved adherence to microscopy test results during the study period involving training on their use (41). In a study in Tanzania to document why clinicians do not follow test results, it was shown that there are three important ‘mindlines’, that is, malaria is easier to diagnose than alternative diseases; malaria is a more acceptable diagnosis; and missing malaria is indefensible. The study showed that it was easier to follow ‘mindlines’ rather than guidelines (42).

Current evidence indicates that no single method for the diagnosis of malaria is perfect nor can any one of them use a stand-alone accurate and effective diagnostic criterion (6).

2.4 Available Treatment Options for Malaria:

Treatment of malaria is generally divided into treatment for severe and uncomplicated malaria. In our country, Kenya, artemether lumefantrine (AL) is the first line while dihydroartemisinin plus piperaquine is used as the second line for uncomplicated malaria. This is in line with WHO recommendations that the second line could either be an alternative Artemisinin-based combination therapy (ACT) or other combinations e.g. quinine plus tetracycline or doxycycline or clindamycin. Treatment of severe malaria involves use of parenteral quinine or parenteral artesunate or artemether. Current recommendations by WHO are in favour of the artesunate, in Kenya this latest policy is being rolled out. Once started the parenteral antimalarial should be continued for at least 24 hours irrespective of ability to take orally. Treatment thereafter can be completed by ACTs, artesunate plus clindamycin or doxycycline; or quinine plus clindamycin or doxycycline. In Kenya usually treatment is completed by use of ACTs (3, 4).

Although the above is the recommendation, antimalarial previously used are still in circulation. Zurovac in two separate studies in Kenya has shown that there was a high likelihood of AL being prescribed in test positive results as opposed to other antimalarial (Fansidar, Amodiaquine), which are still prescribed in test negative results for uncomplicated malaria (17,43). This may however be changing as shown recently by Juma and Zurovac that AL was now commonly prescribed in test negative patients (16).

2.5 Consequences of Over-diagnosis/ Overtreatment of Malaria:

The lack of adherence to test results is itself likely to result in different problems including poor compliance in future as patient will not be satisfied since the antimalarial are not

targeting their problem. In future therefore even when they really have malaria they may not want to use the same drug as they have a bad history with the drugs. Poor compliance is likely to end up with drug resistance a situation also encouraged by using antimalarial when there are no parasites as the patient may get an attack of malaria when having traces of antimalarial in their blood encouraging resistance (3,44). The world is not ready for drug resistance to the current artemisinin derivatives as there are no new molecules available as of now. Shockingly resistance is already being reported in the Thai-Cambodian border, the same area where chloroquine resistance started. This means adherence to the current guideline may be the only saviour, at least for now (18,45,46).

A major concern is that when clinicians treat a patient for malaria, they may not do further work up to establish other causes of the fever. Increased mortality has also resulted from presumptive diagnosis as other diagnoses are not taken into consideration (11).

The diagnosis of malaria clinically has also been associated with increased cost as it is ineffective and ends up with unnecessary wastage of health resources as they are spent on non-malarial cases (6). The cost of treating one malaria case in Kenya is between US dollars 33 to 105 in a district hospital to US dollars 136 in a national hospital (47,48). In a WHO Bulletin though focusing on RDTS versus presumptive treatment noted that, with high cost of antimalarial in use currently, Africa will have no option other than use antibiotics only rather than combining with antimalarial in patients negative for malaria parasites. The same study also showed that microscopy is likely to be cost-effective relative to presumptive treatment with 50% certainty when malaria prevalence is less than 67% and at least 41% prevalence when a 95% certainty is required (49). Zurovac in 2006 although

looking at adults demonstrated that improved clinical practice of adhering to test results of microscopy was cost effective in Kenya (5).

CHAPTER 3: RESEARCH QUESTIONS, OBJECTIVES, AND JUSTIFICATION

3.1 Research Question:

What proportion of admitted children are treated for malaria despite a negative microscopy results for malaria parasites?

3.2 Objectives:

3.2.1 Broad objective:

To describe the clinicians' antimalarial prescription practices for children with negative microscopy results admitted at MTRH.

3.2.2 Specific Objectives:

1. To determine the proportion of children treated for malaria among those with negative microscopy results for malaria parasites admitted at MTRH.
2. To describe the demographic and clinical characteristics associated with antimalarial treatment among children with negative microscopy results for malaria parasites admitted at MTRH.
3. To describe hospital outcomes among children with negative microscopy results for malaria parasites admitted at MTRH.

3.3 Justification of the Study

Majority (86%) of patients treated for malaria at MTRH have either negative or unknown blood slide for malaria parasites test results (10). The sensitivity of microscopy at MTRH is 75% with a specificity of close to 85%, this is far much better than the clinical diagnosis

(10). In various studies, the specificity of clinical diagnosis has been shown to be very low at 0-9% (6).

Lack of adherence to test results is associated with many problems including antimalarial drug resistance. This may result from poor compliance with the antimalarial as patients are not satisfied by the antimalarial drugs since they do not make them feel better because they are not targeting their disease. The drug resistance can also result from the patient subsequently being attacked by malaria when they only have traces of antimalarial (3, 44). The resistance to artemisinin drugs, which was initially reported at the Thai-Cambodian border, and more recently Myanmar and Viet Nam, spells doom for human beings as there are no other new molecules available as yet. Adherence to the current guidelines therefore may be the only saviour for this dire situation (18,21,45,46).

With presumptive treatment, patients are treated for what they do not have and thus mortality is increased (11). Apart from this, there is unnecessary wastage of resources. The cost of treating one case of malaria, including cost of testing, in Kenya is between US dollar 33 and 136 depending on the level of the health facility (47,48). This means therefore that resources will continue to be wasted if we treat patients presumptively for malaria. Microscopy is cost-effective relative to presumptive treatment even when the prevalence of malaria is at least 41% with a 95% certainty. The cost of microscopy was assumed to be US$ 0.32–1.27 (49).

Chandler showed in Tanzania that there was a positive correlation between clinicians training and their practice after completion of medical training as regards malaria diagnosis (43). The Moi Teaching and Referral hospital being a teaching institution would nurture a good practice of adhering to test results and hence have ambassadors to all the hospitals the health workers are posted to after training.

CHAPTER 4: METHODOLOGY

4.1 Study Area:

The Study was carried out at the general paediatrics wards of the Moi Teaching and Referral Hospital (MTRH). MTRH is a national referral hospital serving the Western part of Kenya with a catchment population of approximately 15 million. It is situated in Eldoret town, in Uasin Gishu County. Areas of Rift Valley around MTRH lie under low malaria transmission regions of the country with epidemics likely to occur when temperatures are favourable above 18^{o}C, normally towards the end of the rainy season. The rainy season extends from March to November of every year with June, July and August having low intensity of rainfall. Uasin Gishu County is largely agricultural with Eldoret town being the economic hub of the county.

Although Uasin Gishu County has a low transmission rate for malaria, the other areas surrounding it especially the counties in the former Western and Nyanza provinces have high malaria transmission. It is not uncommon for patients seen at MTRH to have had history of travel to these regions. On the other hand some of the patients seen in MTRH are normally referred from neighbouring hospitals which may have different transmission patterns. Appendix 1, are maps showing the transmission patterns of malaria in areas surrounding MTRH.

MTRH has a bed capacity of 800 with the general paediatric wards having 80 beds and admit an average of 4500 patients per year. The general paediatric wards usually admit children aged between, one (1) month and 14 years.

Children admitted to the paediatrics wards normally have blood slide for malaria parasite done at the sick child clinic in the outpatient department. Routinely thick films are prepared. These slides were taken to the laboratories which serve both children and adults. The slides are prepared using Giemsa stain. The laboratory personnel, including technicians, technologists and parasitologists, then examine blood slides for malaria parasites and estimate the density by counting parasites per microscope field. They then express these in terms of no malaria parasites seen; scanty; + (1 to 9 trophozoites in 100 fields); ++ (1 to 10 trophozoites in 10 fields); +++ (1 to 10 trophozoites per field); or ++++ (>10 trophozoites per field). These results are normally available to the clinicians from 30 minutes of the slides being taken to the laboratory. Some patients get to the wards already with the results while for others the results follow thereafter. This depends mainly on the time the patients arrived to the hospital as the results are normally taken physically to the ward.

Children are sent from the sick child clinic to the paediatric wards where they are reviewed and admitted by the Medical Officer intern and the registrar on duty. The patient is normally reviewed within 24 hours of admission by the paediatrician to evaluate the progress and the treatment.

4.2 Study Population:

The target population constituted children admitted to the general paediatric wards of MTRH, while the study population were those children aged between 1 month and 14 years with negative microscopy results for malaria parasites admitted to the general paediatrics wards and met the following inclusion and exclusion criteria.

Inclusion Criteria:

1. Children admitted with acute onset of clinical features suggestive of malaria (that is, fever, chills, and rigors, difficulty in breathing, diarrhoea, vomiting, anaemia, and yellowness of eyes).
2. Children whose parents/guardians gave consent

Exclusion Criteria:

1. Presence of a known chronic illness (Sickle cell disease, Oncology patients, Heart Diseases)
2. Those with microscopy results for malaria parasites from elsewhere other than MTRH.

4.3 Study Design:

A prospective observational study design was used. This design enabled follow up of patient from admission until discharge noting the hospital outcomes.

4.4 Sample Size:

The Fischer's formulae was used to calculate the minimum sample size for those with negative blood slide.

$$n = \frac{Z^2 \hat{p}(1-\hat{p})}{e^2}$$

n = the sample size= n_o

Z = the standard normal deviation at desired confidence interval (1.96 for 95% confidence level)

$\hat{P}$ = Estimated proportion of children treated for malaria with a negative BS for MPs (23.8%) (Odongo, [10])

e = Desired level of statistical significance (5%)

Replacing these values in the above formulae:

$= \frac{(1.96^2 * 0.238 * 0.762)}{(0.05)^2}$=278.7

Adjusting for finite population for 6 months at MTRH, based on hospital records

An average of 5.6 patients, have a Negative Blood Slide per day.

Thus: $n_{f=\frac{n_0}{1+\frac{n0}{N}}}$ N= 5.6*30*6= 1005, n_o=279

(N= the population size while n_f = is the final sample size)

$n_{f=\frac{279}{1+\frac{279}{1005}}}$ =218.4; Adding 10% for drop out ≈ **241**of Negative Blood Slide patients

4.5 Sampling Technique:

Participants with a negative blood slide for malaria parasites who met inclusion criteria were systematically sampled into the study on all days of the week except weekends and holidays. Considering that a similar period in the first half of 2011 had an average of 5.6 children per day who had a negative blood slide, every 2nd participant who met the

inclusion criteria was enrolled into the study. In case they did not meet the inclusion criteria, the next individual was included. This was continued until the minimum sample size of patients with a negative blood slide was reached.

4.6 Outcome Measures:

The primary outcome measure was proportion of children put on anti-malarial (such as quinine, and Artemisinin-based combination therapy) with a negative microscopy results for malaria parasites.

Secondary outcome measures included: proportion of children put on antibiotics among those treated for malaria, duration of hospital stay, discharge home and death among the study participants.

4.7 Data Collection methods:

Questionnaire: A standard pre-tested questionnaire was used to collect data from inpatient children and their parents/guardian (see Appendix II). It included demographic information, information on the symptoms, treatment sought before coming to MTRH, the physical findings, laboratory information, and treatment given as well as the hospital outcome.

4.8 Execution of the Study:

The data collection was carried out over a period of 6 months between December 2012 and June 2013. The Principal Investigator (PI) had two research assistants (Clinical Officers) who were stationed in the paediatric wards from 8am to 5pm every week day. The research

assistants underwent training on the study so as to make them aware of the children who were to be included in the study. They reviewed children admitted to the paediatric wards on admission to identify those who were eligible and informed the PI. The PI evaluated the children for inclusion into the study within the day of admission and enrolled them into the study. The participants were reviewed after 24 hours of admission and the current treatment recorded including noting whether antimalarial had been stopped and antibiotics had been started. The research assistants monitored the study participants on a daily basis and informed the PI of the death or discharge of each participant. Upon which the duration of hospital stay, and the treatment (antimalarial and antibiotics) at this point were noted. Study participants were followed for a maximum of 30 days after the last recruitment.

4.9 Data management, analysis and Presentation:

Data was entered into a Microsoft Access data base. Data was then checked for consistency by providing validation in Microsoft Access. Data was then exported to STATA version 10 statistical software for analysis. Descriptive statistics such as means, median, interquartile range (IQR) and standard deviation for continuous data and frequency listings for categorical data were used. Chi-square test and logistic regression were used to test for association among qualitative variables. Kruskal-Wallis test was used to compare continuous variables among groups. The key dependent variable was antimalarial prescription and duration of hospital stay, while key independent variable**s** included age, fever, inability to feed, vomiting, diarrhoea, anaemia, prior antimalarial use, and decreased level of consciousness. All analysis were carried out at 95% level of significance. Data has been presented in prose, charts and tables.

4.10 Study Limitations:

Data was collected over 6 months which may have an impact on the quality of data considering malaria has seasonal variation. However, the data was collected over both dry and rainy months thus partially taking care of this limitation.

4.11 Ethical Considerations:

Approval was sought from Institutional Research and Ethics Committee (IREC) of Moi University, College of Health Sciences/MTRH, and permission to conduct the study from the MTRH administration (Appendix III). A written informed consent (Appendix IV) was obtained from the parents/guardian with verbal assent being sought from the children aged 7 years and above. Confidentiality was maintained and participant information de-identified. No coercion or inducements were used to have participants join the study.

CHAPTER 5: RESULTS

5.1 Socio-demographic and Clinical Characteristics of Study Participants

A total of 250 participants were enrolled. The median age of the participants was 19.5 (IQR: 10, 36) months, while the male were 150 (60%) thus a male to female ratio of 1.5:1. Majority of the participants, 225 (90%) were from the Uasin Gishu County. Sixteen percent had history of travel to malaria endemic regions in the preceding 4 weeks. Abnormal respiratory system (RS) examination findings were noted in 34% of the participants as shown in table 1 below.

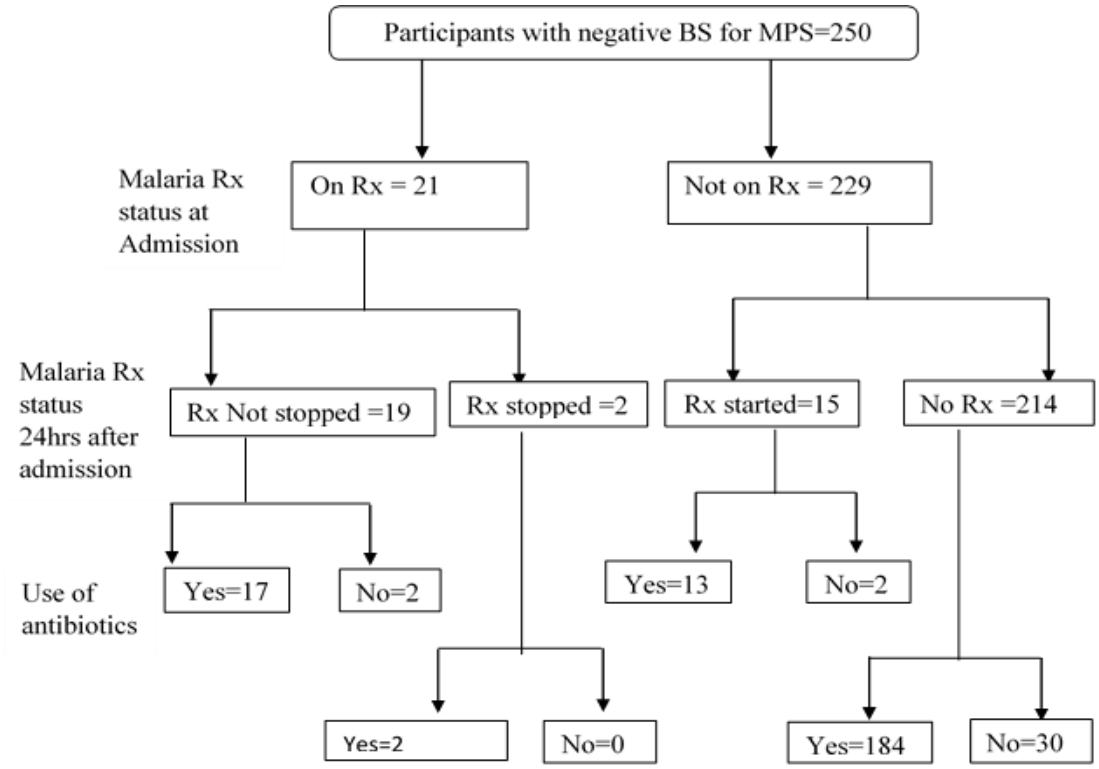
Table 1: The clinical characteristics of the study participants

Variable	**Frequency n=250**	**Percentage (% of n)**
History of Travel[#]: Yes	41	16.4
No	209	83.6
Prior medication with[+]:	30	12.0
Antimalarial		
Antibiotics	60	24.0
Antipyretics	135	54.0
General Condition: Fair	170	68.0
Ill	80	32.0
Level of Consciousness: Alert	249	99.6
Not Alert<A(V,P,U)	1	0.4
Abnormal *CNS*	20	8.0
Systemic *RS*	85	34.0
Examination*: *ENT*	30	12.0
	Median (Interquartile Range)	
Temp (^{o}C)	38.10(37.6,38.1)	
Pulse Rate (per minute)	146(136,159)	
Respiratory Rate (per minute)	30(28,38)	
Duration of Hospital stay (days)	3(3,4)	

#=History of travel to malaria endemic regions.+= Participants having used these drugs prior to coming to MTRH on the day of admission; * Abnormal CNS examination findings included: altered level of consciousness, irritability, confusion and neck stiffness; Ear, Nose and Throat abnormal examination findings included inflamed throat/tonsils. Abnormal respiratory system (RS) examination findings were mainly respiratory distress and added sounds on auscultation.

5.2 Utilization of Laboratory and Microscopy Results for the Participants

Blood slides were requested in outpatient for 244 (96.7%) of the participants. Five (2%) of the participants with negative blood slides had a repeat of the test during their stay in the wards. Of the 250 participants with negative results, 34 (13.6%, [95%CI 9.6, 18.5]) were treated for malaria. This was based on our preset criteria that antimalarial treatment was to constitute those on antimalarial at 24 hours post admission. The distribution of the participants enrolled and their treatment is shown in flow chart in figure 1.



Rx- Treatment

Figure 1: Flow chart of the participants enrolled and the treatment they received

5.3 Socio-demographic and Clinical Characteristics Associated with Treatment for Malaria

Univariate analysis was done to determine the demographic and clinical characteristics of the participants associated with treatment with a test negative microscopy results for

malaria parasites. History of travel to a malaria endemic region and prior use of antimalarial were found to be significantly associated with treatment for malaria among the participants (P Value =0.000). See table 2 below.

Table 2: Socio-demographic and clinical characteristics association with malaria treatment status

Variable*	**Negative- Rx** ***n=34(%)***	**Negative Not-Rx** ***n=216(%)***	**P-Value**[+]
County of Res: UG vs. Others	28(82.4)	192(88.9)	0.645
History of Travel[**]	13(38.2)	28(13.0)	**0.000**
Age: <6mo	1(3.0)	22(10.2)	
6mo-5yrs	22(66.7)	162(75.3)	
>5yrs	10(30.3)	31(14.4)	**0.044**
Sex: M vs. F	17(50.0)	133(61.6)	0.200
History of Fever	33(97.1)	197(91.2)	0.242
History of Inability to feed	11(32.4)	83(38.4)	0.497
History of Vomiting	22(64.7)	107(49.5)	0.100
History of Headache	**10(29.4)**	**12(5.6)**	**0.000**
Hx of Increased Sleepiness	**16(47.1)**	**30(13.9)**	**0.000**
Hx of Diarrhoea/Abd. Pains	18(52.9)	91(42.1)	0.237
Hx of Difficulty in Breathing	4(11.8)	49(22.7)	0.148
History of Cough	**9(26.5)**	**112(51.9)**	**0.006**
History of Convulsions	**10(29.4)**	**31(14.4)**	**0.027**
History of Prior use of **:**			
Antimalarial	**13(38.2)**	**16(7.41)**	**0.000**
Antibiotics	5(14.7)	54(25.0)	0.188
Antipyretics	21(61.8)	114(52.8)	0.327
Gen. Condition: ill Vs. Fair	11(32.4)	69(31.9)	0.976
Presence of Pallor Vs. None	**7(20.6)**	**10(4.6)**	**0.001**
Abnormal CNS Exam	**7(20.6)**	**13(6.0)**	**0.004**
Abnormal RS Exam	8(23.5)	77(35.6)	0.166
Abnormal ENT Exam	6(17.6)	24(11.1)	0.276
	Median (IQR)		**P Value**[#]
Mean Resp Rate	34.08(8.44)		0.534
Mean Pulse Rate	143.26(23.27)		0.511
Mean Temperature	38.21(1.15)		0.977

+= P-value based on Pearson Chi-Square, #=P-value based on Kruskal-Wallis,
*Hx-History; ** History of travel to malaria endemic regions.

A multiple logistic regression on these factors showed that history of prior antimalarial use, history of headache and increased sleepiness were still significant factors independently. No collinearity exist on these factors. See table 3 below.

Table 3: Multiple logistic regressions on clinical characteristics significant on Univariate analysis

Clinical Characteristic	Odds	[95%Conf.	Interval]	P-value
Sex	0.66	0.26	1.66	0.379
History of Travel*	2.10	0.73	6.08	0.171
Age Category	0.92	0.36	2.32	0.854
History of Headache	**4.36**	**1.17**	**16.20**	**0.028**
History of Increased Sleepiness	**4.45**	**1.66**	**11.94**	**0.003**
History of Cough	0.52	0.19	1.40	0.193
History of Convulsions	1.96	0.67	5.67	0.217
Prior Antimalarial use	**7.68**	**2.73**	**21.62**	**0.000**
Presence of pallor	1.75	0.43	7.15	0.436
Abnormal CNS Exam	1.93	0.54	6.94	0.312

* History of travel to malaria endemic regions.

5.4 Antimalarial Prescription Practices

Thirty four participants (13.6%) were treated for malaria with a negative microscopy results. Thirty (88.2%) of these participants had the antimalarial started in the wards. In 19/34 (55.9%) antimalarial prescription occurred at admission. Parenteral antimalarial medication were given in 20/21(95.2%) at admission while 28/34 (82.4%) were still on parenteral antimalarial medication after 24hours.

5.5 Concurrent Antibiotic Prescription Practices

Thirty (88.2%) were also started on antibiotics over and above the antimalarial. Overall 216/250 (85.2%) of all the participants were put on antibiotics. See table 4 below and figure 1 above.

Table 4: Antibiotics Prescription among the participants with negative blood slides for malaria parasites

Variable	Antibiotics n (%)	No Antibiotics n (%)	Odds ratio (95%CI)
Antimalarial	30(88.2)	4(11.8)	
No Antimalarial	186(86.1)	30(13.9)	1.212(0.40-3.68)

Of all the participants treated with antimalarial with negative BS for MPS, 14 (41.18%) completed their antimalarial treatment while in the wards.

5.6 Hospital Outcomes among the Participants

The mean duration of hospital stay was 3.53(2.57) days for those treated while negative versus 3.75(2.21) days for those negative but not treated (P value=0.61).

A sub analysis showed there was no effect of antibiotics on the above hospital stay among those on antimalarial versus those not them (P Value=0.367). However, on the group not put on antimalarial, the presence of antibiotics prolonged their hospital stay significantly (P Value=0.026)

The mortality rate among study participants was 0.4% (1 participant) who was not on antimalarial.

CHAPTER 6: DISCUSSION

Demographic and General Clinical Characteristics:

There were more males than females at 1.5:1. No relationship has been shown between sex and malaria as much as our study only focussed on those with test negative results. In a national survey for malaria in Kenya slightly more females (1.04:1) had been tested for malaria during a febrile episode in the preceding 2 weeks. In a previous study looking at clinical diagnosis of malaria in the same hospital the ratio was 1:1 (10,50). The age distribution is consistent with that of patients likely to be admitted to hospital in our set up. Malaria is known to have highest burden in those less than 5 years although the age below 6 months is associated with less malaria and thus the likely testing as captured in patients recruited (1).

Majority of the patients recruited came from Uasin Gishu County. The proximity of MTRH to inhabitants of this county makes it more likely that they will be captured in such a study. Although MTRH is a referral hospital, it acts as the main hospital for the county. In 2010, Odongo showed 72% of patients were from Uasin Gishu, however their study focussed on patients treated with antimalarial. Patients with chronic illnesses were excluded from the study and this may also have affected the distribution. Sixteen percent of the patients had history of travel to malaria endemic regions in the preceding 4 weeks. The geographical region where MTRH is, is a low malaria endemic region and thus patients with history of travel to malaria regions are more likely to be suspected of having malaria hence the testing (4). This is also demonstrated by the fact that history of travel was significantly associated with treatment of malaria. History of premedication with antimalarial was at 12%, this was

not as high as would be anticipated as a study establishing the level of prescription in outpatient set up showed a high level of 57% of patients with negative blood slides were put on antimalarial (16). However we did not establish whether they had all been started by clinicians or was self-medication. Almost all patients had history of fever or documented fever. This is consistent with current policy guidelines and trends with malaria being more likely to be suspected in such patients hence the testing and therefore recruitment into the study (1,3,4,6,18).

Participants picked for this study had all been tested for malaria as this was an entry criteria. There was a low repeat rate of blood slides which were negative at 2% despite the fact that more than 10% of the participants included ended up being treated for malaria. The policy is to repeat blood slides up to 3 times in 24 hours when malaria is still suspected especially in admitted children (4).

Proportion Treated with Antimalarial:

The rate of treatment with antimalarial for children testing negative for BS for MPs, was substantial at 13.6%. In comparison to other available studies this was however relatively low. Previous studies in East Africa have shown higher values, in 2010, Juma and Zurovac showed that 56.6% of children in Kenya were put on antimalarial with negative blood slides (16). In Tanzania, Reyburn H et.al in various studies has shown least value of 48% (36,37). However, these studies looked at outpatient set up and mainly lower level facilities. These studies had more of a nationwide coverage with both low and high endemicity sites. No studies from inpatient set up were retrievable. The lower value may be attributable to the different set up although other factors may play a role. There is

documented decreasing prevalence of fever attributable to malaria in various countries including Kenya and this may have influenced clinicians decisions (1,19,20). Instructively, most antimalarial were started in the wards and this may mean that only a select subjects with certain factors were being put on antimalarial. As we had highlighted, this study was carried out in wards where registrars in paediatrics (Paediatricians in training) admit patients with post admission ward rounds being done by consultant paediatricians. This may have played a role in having only some select patients being started on antimalarial. On the other hand, even in similar set ups there has been a decrease in presumptive treatment. Zurovac et.al had earlier demonstrated 79% prescription of antimalarial in negative patients in 2006 in Kenya (17). Similarly a review looking at Africa as a whole concluded that presumptive diagnosis was decreasing (20). Changes in policy and treatment guidelines may be responsible for some of these changes. Currently all children should be started only on antimalarial medication if they test positive for malaria (3,4). Adherence to test results has been shown to be a reason for low prescription of antimalarial in those with test negative results as demonstrated in a clinical trial in Tanzania (41). This may have played a role too.

Factors Influencing Treatment with Antimalarial:

Participants' characteristics were analysed in an effort to determine whether any clinical features possibly influenced clinicians to start antimalarial medication in test negative patients. History of travel to malaria endemic regions was significantly associated with treatment with antimalarial. This may have been influenced by known geographical distribution of malaria in Kenya. History of headache, increased sleepiness, convulsions,

and presence of pallor were associated with malaria treatment with presence of cough negatively influencing treatment. Although there is no policy to treat children using clinical algorithms in this hospital, the factors coming out have for long been associated with malaria. In a Gambian study evaluating clinical signs and symptoms predicting malaria, reduced feeding, sleeping and palmar pallor were associated with malaria. Convulsions however were not associated with malaria in that study as were difficulty in breathing, presence of diarrhoea and vomiting. These factors were not different in the group not treated versus that treated with negative results in our study (27). A review of similar clinical features in Kilifi, Kenya at the Coast had only showed pallor and increased sleepiness to be significant in children below 5years (33). These studies were done in high malaria transmission areas. Chandramohan D et.al in India had argued that in low endemic regions, normally fewer factors seem to be associated with malaria clinically. They noted chills, no cough, no runny nose, no diarrhoea, temperature above 37^{o}C, palpable liver and spleen as the factors likely to predict malaria (32). Only lack of cough was similar to what was found in the group treated in our study. Following multiple logistic regression however only prior use of antimalarial, history of headache and increased sleepiness were associated independently with increased chance of treatment in test negative results participants. Among these increased sleepiness has been shown to be associated with clinical diagnosis of malaria as described in the various studies discussed above. Notable, this is what the Kilifi study (33) had found and was thought to be likely to occur in low malaria endemic region. The catchment area of MTRH is largely low endemic especially where majority of the participants came from.

The sensitivity of using clinical symptoms in algorithm to diagnose malaria is high even up to 100% (6). The problem has been specificity. Some authors have argued previously that physician diagnosis on the basis of clinical features without laboratory support has a sensitivity of as high as 89%. The specificity is low also at 20% (32). The previous study in this same hospital by Odongo, showed clinical diagnosis only correctly identified malaria at 3.61%, however there were only 4 patients with PCR proven malaria in that study. On the other hand specificity and sensitivity of microscopy under normal circumstances is not 100%. In MTRH it was shown to be 75% sensitivity and 85% specificity. While one may want to believe this makes clinicians ignore test results, they never do so when results are positive (10,16,17). In a study looking at clinicians view on the utilization of laboratory results at MTRH, clinicians in these wards acknowledged that they trusted the validity of the results; 72.3% and 83.3% of them felt they were reliable and accurate respectively. However, only 50% of these clinicians felt the results influenced their clinical decisions (15). It may therefore be true that clinicians as seen from above followed what appeared to be a logical clinical judgement rather than the test results in starting some participants on antimalarial. However, most of these factors seemed not to be independent when subjected to further analytical processes. Notably though, this study may not have been powered enough to detect this.

Concurrent antibiotic use and hospital outcomes:

Overall 85.2% of all negative patients for BS for MPs received antibiotics. These are significantly higher than what was found in Tanzania by Ngasala et.al who demonstrated 54.3% for those negative in their study received antibiotics (41). In Uganda 39.3% of those

negative for malaria using microscopy received antibiotics in a study done by Batwala et.al (51). These studies were done in outpatient. Similarly however, a previous inpatient study in this same hospital showed a high concurrent prescription of antimalarial and antibiotics at 91.7%. This however included patients with unknown test results for malaria (10). No difference existed in antibiotic prescription between the groups treated with test negative results versus that not treated, 86.1% versus 88.2%. There was no significant differences in the outcome measured between the groups treated with antimalarial versus the negative group not treated. This is in terms of duration of hospital stay, antibiotic prescription and death versus discharge home. The lack of statistically significant difference may be attributed to the fact that most patients were prescribed antibiotics. Similarly, no difference was shown in duration of hospital stay when antibiotics prescription was adjusted for. Notably though, antibiotics seemed to prolong duration of hospital stay in the group not put on antimalarial. This may have masked any possible differences in the outcome of interest. A larger sample size may be necessary to unmask this or prove the lack of it since we know the policy documents, both nationally and internationally, have advocated treatment of test positive treatment only based on likely worse outcomes when there is indiscriminate use of antimalarial (6,12). It is worth noting that in this current study no attempts were made to check the appropriateness of the antibiotics prescribed.

This study sought to assess the utilization of microscopy results in management of malaria in children admitted to paediatric ward. It gives an insight to the fact that the clinicians adhered to test results in majority of patients. In general it appears that there are some known clinical factors which may have tipped clinicians to still go ahead and treat test negative patients with antimalarial. However, most of these factors were not found to be

statistically significant on multiple logistic regression. We recognize that since we did not interview the clinicians directly, the information we derived is mainly inferred. On the other hand, this may reflect the true picture as asking the clinicians their practice may have resulted in them telling us the theory of it.

CHAPTER 7: CONCLUSIONS AND RECOMMENDATIONS

7.1 Conclusions

There was a substantial proportion, 13.6%, of children treated for malaria while having a negative blood slide for malaria parasites results at Moi Teaching and Referral Hospital.

Clinical characteristics that were independently associated with antimalarial prescription for those with negative microscopy results for malaria parasites include; prior use of antimalarial, history of headache and being abnormally sleepy.

There was a high concurrent use of antibiotics and antimalarial among children with negative microscopy results for malaria parasites.

There was no significant difference in hospital outcomes (duration of hospital stay, discharge home or death) for those children treated compared with those not treated with antimalarial while having negative blood slide for malaria parasites.

7.2 Recommendations

1. Efforts need to be made to lower the proportion of children put on antimalarial with negative microscopy results for malaria parasites.
2. A study in our outpatient set up should be done to compare the treatment of children with negative microscopy with that in literature.
3. A qualitative study to establish why clinicians do not adhere to test results in the management of children for malaria should be done.
4. A study is recommended to evaluate whether the use of antibiotics was necessary and possible effect on hospital outcomes.

8.0 REFERENCES:

1. World Health Organization: World malaria report 2013. *Geneva, 2013.*
2. Abuya TO, Molynuex CS, Orago ASS, Were S, Marsh V. Quality of care provided to febrile children presenting in rural private clinics on the Kenyan coast. *Afr Health Sci. 2004; **4**(3): 160-170*
3. World Health Organization: Guidelines for the treatment of malaria – 2nd edition. *Geneva, 2010.*
4. Ministry Of Public Health and Sanitation & Ministry of Medical Services*:* National Guidelines for the Diagnosis, Treatment and Prevention of Malaria in Kenya- 3rd Edition. *Kenya, 2010.*
5. Zurovac D, Larson BA, Akhwale W, Snow RW. The financial and clinical implications of adult malaria diagnosis using microscopy in Kenya. *Trop Med Int Health. 2006; **11**: 1185–1194.*
6. Chipeta J, Mharakurwa S, Thuma P, Kumar N. A Synopsis of Current Malaria Diagnosis Trends. *Med J Zambia 2009; **36**(2).*
7. Msellem MI, Mårtensson A, Rotllant G, Bhattarai A, Strömberg J, Kahigwa E, et.al. Influence of Rapid Malaria Diagnostic Tests on Treatment and Health Outcome in Fever Patients, Zanzibar—A Crossover Validation Study. *PLoS Med. 2009 April; **6**(4):*
8. Kyabayinze DJ, Asiimwe C, Nakanjako D, Nabakooza J, Counihan H, Tibenderana JK. Use of RDTs to improve malaria diagnosis and fever case management at primary health care facilities in Uganda. *Malar J. 2010; **9**: 200.*

9. Derua YA, Ishengoma DRS, Rwegoshora RT, Tenu F, Massaga JJ, Mboera LEG, Magesa SM. Users' and health service providers' perception on quality of laboratory malaria diagnosis in Tanzania. *Malar J. 2011; **10**: 78.*
10. Odongo FO. Laboratory Diagnostic Outcome of In-Patient Children Treated for Malaria at The Moi Teaching And Referral Hospital, Eldoret, Kenya. *Unpublished MMed Thesis, Moi University. 2011.*
11. Reyburn H, Mbatia R, Drakeley C, Carneiro I, Mwakasungula E, Mwerinde O. et.al Overdiagnosis of malaria in patients with severe febrile illness in Tanzania: a prospective study. *BMJ 2004; **329**:1212–5.*
12. World Health Organization: Global plan for resistance containment (GPARC). *Geneva, 2011.*
13. Njama-Meya D, Clark TD, Nzarubara B, Staedke S, Kamya MR, Dorsey G. Treatment of malaria restricted to laboratory-confirmed cases: a prospective cohort study in Ugandan children. *Malar J.* 2007, ***6***:*7.*
14. Barat LM, Chipipa J, Kolczak M, Sukwa T. Does the availability of blood slide microscopy for malaria at health centers improve the management of persons with fever in Zambia? *Am J of Trop Med Hyg 1999; **60**: 1024–1030.*
15. Marete IK, Osiemo-Lagat Z, Simba JM, Obala A, Muriithi GM, Chumba JC, et.al Utilization of Laboratory Services in Management of Febrile Children at A Referral Hospital in Kenya: A Clinicians' View. *Kenya J. Health Sci. 2013;**2**:28-32.*
16. Juma E, Zurovac D. Changes in health workers' malaria diagnosis and treatment practices in Kenya. *Malar J.* 2011; ***10**:1*

17. Zurovac D, Midia B, Ochola SA, English M, Snow RW. Microscopy and outpatient malaria case management among older children and adults in Kenya. *Trop Med Int Health. 2006; **11**: 432–440.*

18. Malaria, Fact sheet, *World Health Organization, 2013 December; **94.***

19. Okiro EA, Hay SI, Gikandi PW, Sharif SK, Noor AM, Peshu N, Marsh K, et.al. The decline in paediatric malaria admissions on the coast of Kenya *Malar J. 2007; **6**: 151.*

20. D'Acremont V, Lengeler C, Genton B. Reduction in the proportion of fevers associated with *Plasmodium falciparum* parasitaemia in Africa: a systematic review. *Malar J. 2010; **9**: 240.*

21. World Health Organization: World malaria report 2011. *Geneva, 2011.*

22. Kenya National Bureau of Statistics (KNBS) and ICF Macro. Kenya Demographic and Health Survey 2008-09. Calverton, Maryland: *KNBS and ICF Macro. 2010.*

23. George IO, Ewelike-Ezeani CS, Haematological changes in children with malaria infection in Nigeria. *JMMS 2011; **2**(4).768-771.*

24. Kassa D, Petros B, Messele T, Admassu A, Adugna F, Wolday D. Parasito-haematological features of acute *Plasmodium falciparum* and *P. vivax* malaria patients with and without HIV co-infection at Wonji Sugar Estate, Ethiopia. *Ethiop.J.Health Dev. 2005; **19**(2).*

25. Pasvol G, The treatment of complicated and severe malaria. *Br Med Bull2005; **75-76**(1): 29-47.*

26. Malaria and HIV interactions and their implications for public health policy. *World Health Organization 2010.*

27. Bojang KA, Obaro S, Morison LA, Greenwood BM. A prospective evaluation of a clinical algorithm for the diagnosis of malaria in Gambian children. *Trop Med Int Health. 2000; **5**: 231–236.*

28. Taylor SM, Molyneux ME, Simel DL, Meshnick SR, Juliano JJ, Does this patient have malaria? *JAMA. 2010 Nov 10; **304**(18):2048-56.*

29. Hänscheid T, Längin M, Lell B, Pötschke M, Oyakhirome S, Kremsner PG, et al. Full blood count and haemozoin-containing leukocytes in children with malaria: diagnostic value and association with disease severity. *Malar J. 2008; **7**: 109.*

30. Nkuo-Akenji TK, Chi PC, Cho JF, Ndamukong KK, Sumbele I. Malaria and helminth co-infection in children living in a malaria endemic setting of mount Cameroon and predictors of anemia. *J Parasitol. 2006 Dec; **92**(6):1191-5.*

31. Olaleye BO, Williams LA, D'Alessandro U, Weber MM, Mulholland K, Okorie C, et.al. Clinical predictors of malaria in Gambian children with fever or a history of fever. *Trans. R. Soc. Trop. Med. Hyg. 1998; **92**, 300–304.*

32. Chandramohan D, Jaffar S, Greenwood B. Use of clinical algorithms for diagnosing malaria. *Trop Med Int Health. 2002; **7**: 45–52.*

33. Mwangi TW, Mohammed M, Dayo H, Snow RW, Marsh K. Clinical algorithms for malaria diagnosis lack utility among people of different age groups. *Trop Med Int Health. 2005 Jun; **10**(6): 530–536.*

34. World Health Organization: WHO Technical Updates on Malaria Policies. *Geneva, 2010.*

35. World Health Organization: Malaria Microscopy Quality Assurance Manual, *Geneva 2008*

36. Reyburn H, Ruanda J, Mwerinde O, Drakeley C. The contribution of microscopy to targeting antimalarial treatment in a low transmission area of Tanzania. *Malar J. 2006, **5**:4.*

37. Reyburn H, Mbakilwa H, Mwangi R, Mwerinde O, Olomi R, Drakeley C, et al. Rapid diagnostic tests compared with malaria microscopy for guiding outpatient treatment of febrile illness in Tanzania: randomised trial. *BMJ 2007, **334**:403.*

38. Chinkhumba J, Skarbinski J, Chilima B, Campbell C, Ewing V, San Joaquin M, et al, Comparative field performance and adherence to test results of four malaria rapid diagnostic tests among febrile patients more than five years of age in Blantyre, Malawi. *Malar J. 2010 Jul 20; **9**:209.*

39. Nankabirwa J, Zurovac D, Njogu JN, Rwakimari JB, Counihan H, Snow RW, et.al. Malaria misdiagnosis in Uganda - implications for policy change. *Malar J 2009, **8**:66.*

40. Okebe UJ, Walther B, Bojang K, Drammeh S, Schellenberg D, Conway DJ, et.al. Prescribing practice for malaria following introduction of artemether-lumefantrine in an urban area with declining endemicity in West Africa. *Malar J. 2010, **9**:180.*

41. Ngasala B, Mubi M, Warsame M, Petzold MG, Massele AY, Gustafsson LL, et.al. Impact of training in clinical and microscopy diagnosis of childhood malaria on antimalarial drug prescription and health outcome at primary health care level in Tanzania: A randomized controlled trial. *Malar J. 2008; **7**: 199.*

42. Chandler IRC, Jones C, Boniface G, Juma K, Reyburn H, Whitty CJM. Guidelines and mindlines: why do clinical staff over-diagnose malaria in Tanzania? A qualitative study. *Malar J. 2008; **7**: 53.*

43. Zurovac D, Njogu J, Akhwale W, Hamer DH, Larson BA, Snow RW. Effects of revised diagnostic recommendations on malaria treatment practices across age groups in Kenya. *Trop Med Int Health. 2008; **13**: 784–787.*

44. Kokwaro, G., Ongoing challenges in the management of malaria. *Malar J. 2009, **8**(Suppl 1):S2.*

45. Noedl H, Se Y, Schaecher K, Smith BL, Socheat D, Fukuda MM. Evidence of Artemisinin-Resistant Malaria in Western Cambodia. *N Engl J Med 2008; **359**:2619-2620.*

46. Dondorp MA, Nosten F, Yi P, Das D, Phyo AP, Tarning J, et al. Artemisinin Resistance in Plasmodium falciparum Malaria. *N Engl J Med 2009; **361**:455-467.*

47. Kirigia JM, Snow RW, Fox-Rushby J, Mills A. The cost of treating paediatric malaria admissions and the potential impact of insecticide-treated mosquito nets on hospital expenditure. *Trop Med Int Health. 1998 Feb; **3**(2):145-50.*

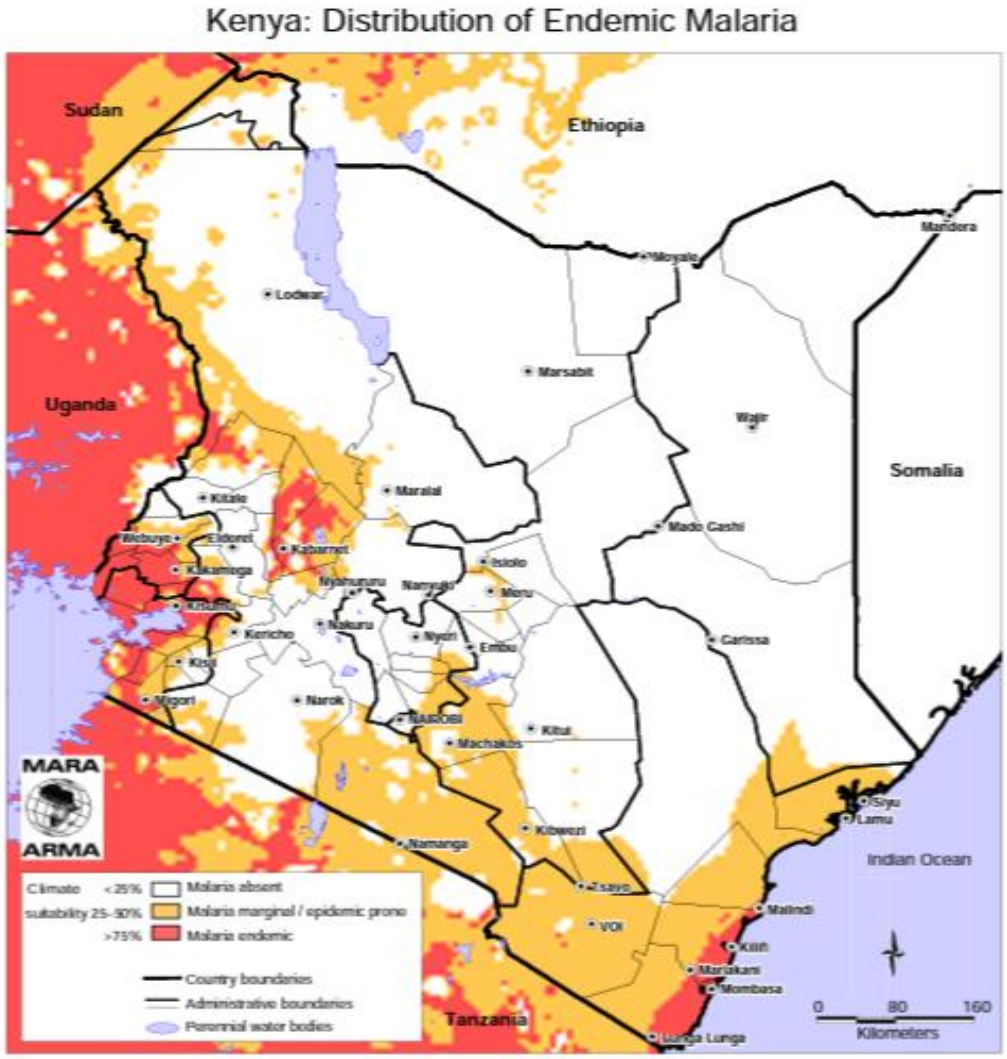
48. Ayieko P, Akumu AO, Griffiths UK, English M. The economic burden of inpatient paediatric care in Kenya: household and provider costs for treatment of pneumonia, malaria and meningitis. *Cost Eff Resour Alloc. 2009; **7**:3.*

49. Shillcutt S, Morel C, Goodman C,Coleman P, Bell D, Whitty CJM, et al. Cost-effectiveness of malaria diagnostic methods in sub-Saharan Africa in an era of combination therapy. *Bull World Health Organ. 2008 Feb; **86**(2): 101–110*

50. Division of Malaria Control [Ministry of Public Health and Sanitation], Kenya National Bureau of Statistics, and ICF Macro. 2011. *Kenya Malaria Indicator Survey. Nairobi, Kenya: DOMC, KNBS and ICF Macro. 2010*

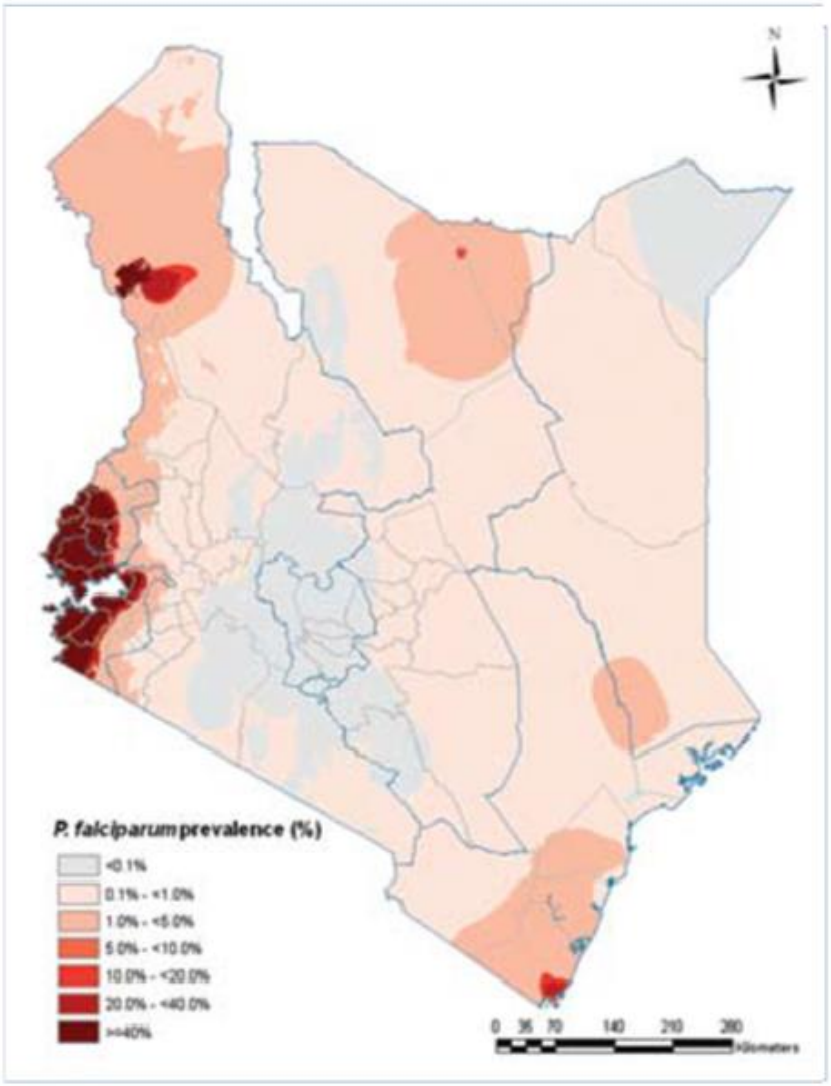
51. Batwala V, Magnussen P, Nuwaha F, Antibiotic use among patients with febrile illness in a low malaria endemicity setting in Uganda. *Malar J. 2011; **10**:377*

Appendix I: Kenyan Maps Showing Malaria Distribution



This map is a product of the MARA/ARMA collaboration (http://www.mara.org.za). July 2005. Medical Research Council, PO Box 70380, Overport, 4067, Durban, South Africa
CORE FUNDERS of MARA/ARMA: International Development Research Centre, Canada (IDRC); The Wellcome Trust UK; South African Medical Research Council (MRC);
Swiss Tropical Institute, Multilateral Initiative on Malaria (MIM) / Special Programme for Research & Training in Tropical Diseases (TDR); Roll Back Malaria (RBM).
Malaria distribution model: Craig, M.H. et al. 1999. Parasitology Today 15: 105-111.
Topographical data: African Data Sampler, WRI, http://www.igc.org/wri/sdis/maps/ads/ads_idx.htm.

2009 Kenya malaria endemicity map-



Abdisalan M Noor et al. The risks of malaria infection in Kenya in 2009 BMC Infectious Diseases 2009, 9:180

Note: The 2005 map with location of Eldoret while the 2009 map has more details on the transmission patterns

Appendix II: Questionnaire

Clinicians' Utilization of Microscopy Results in Management of Malaria among Children admitted at the Moi Teaching and Referral Hospital, Kenya
Study No……. IP No…….

A: At Admission:

I: Demographic data:

1. Age: ……Yrs……..Months…….Days. 2. Sex: 1.Male [] 2.Female []
3. Informant Relationship with Patient:
4. Area of Residence:……County. (*Residence in the Preceding Month*)
5. (a) History of Travel: Yes [ ] No [ ] If Yes 5(b) Where..... and 5(c) How long ago..... Weeks

II: Clinical Presentation:

a) History and duration of presenting symptoms:

Symptom: (*for each of the symptom if present indicate duration in days before admission*)

1. Fever1.Yes [] 2.No [] Duration……
2. Inability to feed1.Yes [] 2.No [] Duration……..
3. Vomiting1.Yes [] 2.No [] Duration…….
4. Headache1.Yes [] 2.No [] Duration……
5. Chills/Shaking/Sweating/Easy fatigability 1.Yes [] 2.No [] Duration……
6. Increased Sleepiness/Malaise 1.Yes [] 2.No [] Duration……..
7. Diarrhoea/Abdominal pains1.Yes [] 2.No [] Duration……
8. Joint Pains 1.Yes [] 2.No [] Duration……...
9. Difficulty in breathing 1.Yes [] 2.No [] Duration……
10. Cough 1.Yes [] 2.No [] Duration……
11. Pain on passing urine 1.Yes [] 2.No [ ] Duration……
12. Yellowness of the eyes 1.Yes [] 2.No [] Duration……
13. Convulsions: 1. Yes [ ] 2. No [ ] Duration.....

b) Prior Medical Intervention and duration used:

1. (a) Antimalarial: 1.Yes [] 2.No [ ] Specify (……) Duration [ ] Days;
(b)Treatment Completed: 1.Yes [] 2.No []
2(a) Antibiotics: 1.Yes [] 2.No [ ] Specify (……) Duration [ ] Days;
(b)Treatment Completed: 1.Yes [] 2.No []
3(a) Antipyretics: 1.Yes [] 2.No [ ] Specify (……) Duration [ ] Days;

c) Physical Examination Findings:

General Examination:
1. Level of Consciousness: 1.A [ ] 2.V [] 3.P [] 4.U []
2. General Condition: 1.Ill-looking [ ], 2.Fair [] 3. Good [ ]
3. Pallor: 1.None [] 2.Mild [ ] 3.Moderate [] 4.Severe [] 4.Jaundice1.Yes [] 2.No []
5. Edema: 1.Yes [] 2. No [] Presence of a rash 1.Yes [] 2. No []
6. Wt: ..... Kg; 7. Ht: ..... Cm

Vital Signs:
8. PR……..bpm. 9. RR……..bpm.10. Temperature …… ^{o}c.:

Systemic Findings
11. CNS: 1.Normal [], 2.Abnormal []; If Abnormal
Specify……..
12. CVS: 1. Normal [], 2. Abnormal []; If Abnormal
Specify……
13. RS: 1. Normal [], 2. Abnormal []; If Abnormal
Specify……
14. P/A: 1.Normal [], 2.Abnormal []; If Abnormal
Specify……
15. ENT: 1.Normal [], 2.Abnormal []; If Abnormal
Specify……..

d) Laboratory Findings:

Blood Slide for malaria Parasite

1(a) Requested in: 1.Casualty [ ] 2.Wards [ ] 1(b) Results: 1.Positive [ ] 2.Negative [ ]
1(c) If the above was positive, how did the lab report it: 1.Scanty [ ], 2.**1+** [ ], 3.**2+** [], 4.**3+** [], 5.**4+** []
2. Any repeat BS for MPs in the wards? 1. Yes [ ] 2.No [ ], Indicate Results and Day
……

e) **Treatment Given:**

1(a) Antimalarial: Yes [ ] No [ ]
1(b) If Yes: Parenteral: Quinine1. IM [] 2.IV []
Artesunate1. IM [] 2.IV []
Others specify.....
Oral: 1.AL [ ]
2. Quinine [ ]
Others specify.....
1(c) Where were they started 1. Wards [ ]; 2.Casualty [ ]
1 (d) If started in the casualty, was it stopped if Blood Slide for malaria parasites results was negative in the wards? 1. Yes [], 2.No []
2(a) Antibiotics: 1. Yes [ ] 2.No [ ]
2(b) If yes above, where were they started? 1. Casualty [ ] 2. In the wards [ ]

B: At 24 Hours:

1(a) Is the patient still on antimalarial? Yes [ ] No [ ]
1(b) If Yes which ones?
Parenteral: Quinine1. IM [ ] 2.IV [ ]
Artesunate1. IM [ ] 2.IV [ ]
Others specify.....
Oral: 1.AL [ ]
2. Quinine [ ]
Others specify.....
2(a). Is the patient concurrently on antibiotics? Yes [ ] No [ ]
2(b) If yes, which one?.....

C: At Discharge:

1. What was the discharge diagnosis? ……

2. What was the duration of stay: [ ] days
3. If patient was on antimalarial, did they complete course of treatment? Yes[ ] No[ ]
4. Were antibiotics concurrently used with antimalarial? Yes [ ] No [ ]
5. Outcome: 1. Discharge Home, [ ] 2. Death [ ]

Appendix III: Ethical Approval Documents

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471/2/3

MOI UNIVERSITY
SCHOOL OF MEDICINE
P.O. BOX 4606
ELDORET
Tel: 33471/2/3

Reference: IREC/2012/157
Approval Number: 000878

30th August, 2012

Dr. Justus Simba Maingi,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

Dear Dr. Simba,

RE: FORMAL APPROVAL

The Institutional Research and Ethics Committee have reviewed your research proposal titled:

"Clinicians' Utilization of Microscopy Results in Management of Malaria among Children Admitted at the Moi Teaching and Referral Hospital, Kenya."

Your proposal has been granted a Formal Approval Number: **FAN: IREC 000878** on 30th August, 2012. You are therefore permitted to begin your investigations.

Note that this approval is for 1 year; it will thus expire on 29th August, 2013. If it is necessary to continue with this research beyond the expiry date, a request for continuation should be made in writing to IREC Secretariat two months prior to the expiry date.

You are required to submit progress report(s) regularly as dictated by your proposal. Furthermore, you must notify the Committee of any proposal change (s) or amendment (s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. The Committee expects to receive a final report at the end of the study.

Yours Sincerely,

PROF. E. WERE
CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

APPROVED
30 AUG 2012
P.O. BOX 4606 ELDORET

cc:
Director	-	MTRH
Principal	-	CHS
Dean	-	SOM
Dean	-	SPH
Dean	-	SON
Dean	-	SOD

MOI TEACHING AND REFERRAL HOSPITAL

Telephone: 2033471/2/3/4
Fax: 61749
Email: director@mtrh.or.ke
P. O. Box 3
ELDORET

Ref: ELD/MTRH/R.6/VOL.II/2008

13th September, 2012

Dr. Justus Simba Maingi,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

RE: APPROVAL TO CONDUCT RESEARCH AT MTRH

Upon obtaining approval from the Institutional Research and Ethics Committee (IREC) to conduct your research proposal titled:

"Clinicians' Utilization of Microscopy Results in Management of Malaria among Children Admitted at the Moi Teaching and Referral Hospital, Kenya."

You are hereby permitted to commence your investigation at Moi Teaching and Referral Hospital.

DR. J. KIBOSIA
DIRECTOR
MOI TEACHING AND REFERRAL HOSPITAL

CC - Deputy Director (CS)
- Chief Nurse
- HOD, HRISM

Appendix IV: Consent

Consent Form for the Parent/Guardian of Child Involved in Utilization of Microscopy study.

We are conducting a study titled: *Clinicians' Utilization of Microscopy Results in Management of Malaria among Children admitted to the Moi Teaching and Referral Hospital, Kenya*

This study involves getting clinical information of your child either by directly asking you/examining the child or looking at the file. We do not intend to carry out any extra test on your child apart from those the primary doctor seeing you will request.

We intend to compare the findings from this study and possibly influence future policies on management of malaria. There is no direct benefit for participating in this study.

We therefore request your permission to involve your child in this study. Refusing to participate in this study will not affect the management of your child.

If you have any questions which you feel the investigator explaining to you has not handled or you would want another opinion, feel free to contact the **Principal Investigator, Dr. Simba, Justus 0723114529**

I have understood the explanation given to me about this study and hereby give consent for my child to take part in it'

Name: ……Signature……. Date ……..

Investigator:

Name..... Signature .....Date.....

Witness:

Name: …….. Signature ……. Date ……