

**UNCOMPLICATED MALARIA CASE MANAGEMENT PRACTICES USING  
ARTEMETHER-LUMEFANTRINE IN SETTINGS WITHOUT MICROSCOPY IN  
UNDERFIVES IN KIBAHA AND KISARAWA DISTRICTS, 2009.**

**Siril M.K. Michael (MD)**

**A dissertation submitted in partial fulfilment of the requirements for the degree  
of Master of Science in Tropical Diseases Control  
Muhimbili University of Health and Allied Sciences.**

**July, 2010**

## ABSTRACT

Tanzania has high burden of morbidity and mortality caused by malaria which is the leading cause of outpatients, inpatients, and admissions of children less than five years of age at health facilities in the country. This burden has been attributed to increasing malaria parasite resistance to most of the antimalarials used as monotherapies. Tanzania has amended the malaria treatment policy twice, the first amendment being in August 2001 when SP replaced chloroquine and the second being in January 2007 when artemether-lumefantrine (Alu) replaced SP for the treatment of uncomplicated malaria. The goal of the amendments was to reduce morbidity, mortality and economic losses and to encourage rational drug use in order to minimize the development of drug resistance. Resistance can develop if artemisinin combination therapies (ACTs) are used unjudiciously as in presumptive diagnosis and treatment of malaria, which is the case in many health care facilities. There are very few reports on the quality of clinical practices following implementation of Alu policies in Africa in general and Tanzania in particular. Furthermore, it is not known what percentage of children suffering from uncomplicated malaria receive ACTs on clinical grounds while in fact they have or have no malaria as confirmed by laboratory diagnosis.

The aim of this study was to examine the quality of childhood malaria case management practices using Alu and the accuracy of clinical malaria diagnosis in settings without microscopy.

Health care facility-based, cross-sectional, cluster random sample survey was conducted in 17 government health facilities to examine uncomplicated malaria case management practices using artemether-lumefantrine in settings without microscopy in underfives in Kibaha and Kisarawe districts.

**CERTIFICATION**

The undersigned certifies that he has read and hereby recommends for acceptance a dissertation entitled: **Uncomplicated Malaria Case Management Practices Using Artemether-Lumefantrine in Settings Without Microscopy in Underfives in Kibaha and Kisarawe Districts, 2009** in partial fulfilment of the requirements for the degree of Master of Science in Tropical Diseases Control Muhimbili University of Health and Allied Sciences.

**PROF CHARLES M. KIHAMIA**

.....  
  
Supervisor

Date.....02/07/2010

Using structured questionnaires data were collected and analysed from 916 children aged less than 5 years who were brought to the health facilities with history of fever and/or other symptoms of malaria. Blood smears to detect the presence of malaria parasites were taken from the selected children and were subsequently processed and examined in the Medical Parasitology Laboratory at Muhimbili University of Health and Allied Sciences.

Of the 916 caregivers of underfive children, 469 (51.2%) sought care within 24 hours of onset of symptoms and 572 (64.6%) knew correctly more than 3 uncomplicated malaria symptoms in underfives. This knowledge was associated with early care seeking (OR= 1.4, 95%CI: 1.2-1.7). Moderate to high socioeconomic status was associated with increasing knowledge of symptoms of uncomplicated malaria in underfives as well as knowledge on correct use of Alu under directly observed therapy and subsequent use at home (OR=3.6, 95%CI: 1.5-9.2).

Malaria was suspected in 846 children (92.4%), 527 of whom (62.3%; 95%CI (58.9-65.6) were appropriately managed according to IMCI and malaria treatment guidelines. Suspected malaria cases were more likely to receive appropriate management than those who had not been diagnosed to have malaria (OR= 36.9, 95%CI: 16 to 118). Presence of fever or history of fever as main presenting symptom was significantly associated with the quality of management given to the patients (OR = 20, 95%CI :6-68).

Of 723 children who were prescribed with Alu, 459 (63.5%) were properly counseled. Alu was more likely to be prescribed in consultations by a clinical officer (OR=1.2, 95%CI: 1.06-1.8); which took more than 5 minutes (OR=1.9, 95%CI:1.3-3.0), and where Alu alone was available as an antimalarial (OR= 1.4, 95%CI:1.05-1.8) than in consultations by non clinical officers, which took less than 5 minutes and where alu and other antimalarials were available. Quality of counselling was associated with the counselling by the clinical officer (OR=1.4, 95%CI: 1.2-1.5) and with the counseling by a provider with above 2 years of working experience (OR=1.5, 95%CI: 1.3-1.7).



Of the suspected malaria cases, 179 (26.0 %, 95%CI: 22.8-29.5) had laboratory confirmed malaria. With PPV=26%, post-test probability of absence of disease in clinically positive malaria = 74% and NPV = 88.5%, post-test probability of presence of malaria parasites in clinically negative malaria = 11.5%.  $LR^+ >1$  (1.06) and  $LR^- <1$  (0.4).

Early care seeking, clinical diagnosis and treatment of malaria using Alu in underfives in settings without microscopy has not reached the set target of appropriately managing 80% malaria in children by 2010. A lot of misdiagnosis and mistreatment with antimalarials well as omission of true cases of malaria calls for swift deployment of specific and sensitive diagnostic facilities.

## TABLE OF CONTENTS

CERTIFICATION .....	ii
ABSTRACT .....	iii
TABLE OF CONTENTS .....	vi
LIST OF ABBREVIATIONS .....	viii
LIST OF FIGURES AND TABLES .....	x
DEDICATION .....	xi
ACKNOWLEDGEMENTS .....	xii
DECLARATION.....	xiv
COPYRIGHT .....	xv
CHAPTER 1 .....	1
1.0 INTRODUCTION AND LITERATURE REVIEW .....	1
1.1 Global malaria burden .....	1
1.2 Malaria burden in Africa .....	1
1.3 Malaria burden in Tanzania.....	2
1.4 Roll back malaria and role of chemotherapy.....	3
1.5 Malaria case management in children aged less than 5 years .....	10
CHAPTER 2.....	21
2.0 PROBLEM STATEMENT AND STUDY JUSTIFICATION .....	21
CHAPTER 3.....	23
3.0 RESEARCH QUESTIONS AND OBJECTIVES.....	23
3.1 General research questions .....	23
3.2 Specific research questions.....	23
3.3 Broad objective.....	24
3.4 Specific objectives.....	24
CHAPTER 4.....	25
4.0 METHODOLOGY .....	25
4.1 The survey setting.....	25
4.2 Data collection.....	30

4.3 Quality control .....	32
4.4 Working definitions .....	32
4.5 Study variables .....	36
4.6 Pre-testing of research tools .....	37
4.7 Data management and statistical analysis .....	37
4.8 Study limitations and sources of error .....	38
4.9 Ethical issues .....	39
CHAPTER 5 .....	40
5.0 RESULTS .....	40
5.1 Enrolment .....	40
5.2 Health care providers and health care facility characteristics .....	40
5.3 Characteristics of the studied children and their caregivers .....	41
5.4 Caregivers' knowledge .....	44
5.5 Quality of case management and prescription of antimalarials .....	49
5.6 Comparison of clinical malaria diagnosis and laboratory confirmed diagnosis .....	53
CHAPTER 6 .....	57
6.0 DISCUSSION .....	57
6.1 Factors affecting the quality of care, prescription of Alu and other antimalarials .....	58
6.2 Factors affecting early care seeking .....	59
6.3 Knowledge of malaria symptoms and correct use of Alu in underfive year children among the caregivers .....	60
6.4 Malaria infection among those who had laboratory confirmed diagnosis .....	61
6.5 Child's age, infection and quality of care and antimalarial prescription .....	62
CHAPTER 7 .....	64
7.0 CONCLUSIONS AND RECOMMENDATIONS .....	64
7.1 Conclusions .....	64
7.2 Recommendations .....	66
REFERENCES .....	67

APPENDICES .....	80
Appendix 1 English Version of the Questionnaire.....	80
Appendix 2 Swahili version of the questionnaire.....	89
Appendix 3 Procedures for laboratory malaria diagnosis .....	95
Appendix 4 Maps, figures and tables .....	97

**LIST OF ABBREVIATIONS**

ACTs	= Artemisinin-Based Combination Therapies
AIDS	= Acquired Immuno Deficiency Syndrome
ALRI	= Acute Lower Respiratory Tract Infections
ALu	= Artemether-Lumefantrine
BC	= Before Christ
CDC	= Centre for Disease Control
CI	= Confidence Intervals
DHMT	= District Health Management Team
DHS	= Demographic Health Surveys
DMO	= District Medical Officer
EDT	= Early Diagnosis and Treatment
GFATM	= Global Fund to Fight Aids, Tuberculosis and Malaria
IMCI	= Integrated Management of Childhood Illness
IPT	= Intermittent Preventive Treatment
IRS	= Indoor Residual Spraying
ITNs	= Insecticide-Treated Nets
LLIN	= Long-Lasting Insecticidal Nets
MSc	= Master of Science
MSD	= Medical Store Department
MUHAS	= Muhimbili University of Health and Allied Sciences
NMCP	= National Malaria Control Programme
OR	= Odds Ratio
RBM	= Roll Back Malaria
RDT	= Rapid Diagnostic Tests
RMO	= Regional Medical Officer
SP	= Sulfadoxine–Pyrimethamine
TDC	= Tropical Disease Control
USA	= United States of America



WBC = White Blood Cells

WHO = World Health Organization

### LIST OF FIGURES AND TABLES

Table 1	Study variables .....	36
Table 2a	Baseline characteristics of 916 studied children.....	42
Table 2b	Baseline characteristics of the caregivers.....	42
Table 3a	Knowledge of the caregivers and care seeking .....	44
Table 3b	Illness attributes and care of the children.....	45
Table 4	Factors affecting care giver's knowledge on malaria symptoms .....	46
Table 5	Factors affecting knowledge on Alu use .....	47
Table 6	Factors affecting early care seeking by the care givers.....	48
Table 7	Quality of malaria case management by malaria diagnosis category .....	50
Table 8	Factors affecting appropriate malaria case management among those who had presumptive malaria diagnosis .....	51
Table 9	Factors affecting prescription of Alu.....	52
Table 10	Laboratory confirmed malaria diagnosis by age and clinical.....	53
	presentation (n=750).....	53
Table 11	Parasite count by age (n=750).....	54
Table 12	Children with laboratory confirmed malaria who were given antimalarials.....	54
Table 13	Comparison of clinical and laboratory diagnosis of malaria.....	56

**DEDICATION**

This dissertation is dedicated to my dear wife Dr Apansia, my dear son Nathaniel, my highly esteemed teachers and my beloved parents.

## ACKNOWLEDGEMENTS

I would like first and foremost to express my heartfelt gratitude to my supervisor Professor Charles M. Kihamia from the Department of Parasitology and Medical Entomology, Muhimbili University of Health and Allied Sciences for his interest, encouragement and tireless guidance from the beginning and designing of this research work to its completion; and Professor Karim Hirji (co-supervisor) from the Department of Epidemiology/Biostatistics, Muhimbili University of Health and Allied Sciences for his indispensable guidance in the design, implementation of the workplan and data management.

Special thanks to Professor Zul Premji and Dr D Tarimo for their indispensable advice, support and guidance throughout my study and development of this research work and Dr Rose Mpembeni for her invaluable advice on data analysis and presentation. The Government of the United Republic of Tanzania through the Ministry of Health and Social Welfare sponsored the entire course and gave me permission to conduct this research in its health facilities. The financial support towards development and final production of this research work and dissemination of the report was kindly provided by the National Institute for Medical Research through its Health Research Users' Trust Fund (Project No 01.2009), to which I am sincerely grateful and highly indebted.

I am also deeply indebted to the authorities of the Coast region and Kibaha and Kisarawe districts for facilitation of my study in the health facilities and the staff of the visited health facilities in the said districts for their cooperation and support during the period of data collection.

My appreciation also goes to staff of the Department of Parasitology and Medical Entomology of Muhimbili University of Health and Allied Sciences specifically Mr Lucas Mahikwano for assisting me with laboratory work and all my fellow students for their various contributions towards the completion of this work.


Finally but not least my earnest appreciation goes to my dear wife Dr Apansia and my lovely son Nathaniel for their support, prayers and encouragement.

For all of you, your contributions will always be cherished and remembered.



**DECLARATION**

I, **Siril M.K Michael**, declare that this dissertation is my own original work and that it has not been presented and will not be presented to any other University for a similar or any other degree award.

Signature .....  .....

Date .....  .....

### **COPYRIGHT**

This dissertation is copyright material protected under the Copyright Act of 1999 and other international and national enactments, in that it may not be reproduced by any means in full or in part except for short extracts in fair dealings, for research or private study, critical scholarly review or discourse with an acknowledgement, without the written permission of the Directorate of Postgraduate Studies, on behalf of both the author and the Muhimbili University of Health and Allied Sciences.

## CHAPTER 1

### 1.0 INTRODUCTION AND LITERATURE REVIEW

Malaria, an ancient parasitic disease, thought to have evolved with the mankind, has been known to us for millennia, with written accounts of similar fevers first appearing around 6000 BC. It is a vector-borne infectious disease caused by protozoan parasites of the genus *Plasmodium* which are transmitted from man to man by blood sucking female *Anopheles* mosquitoes.

Four types of the *Plasmodium* parasites infect humans. These are *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malariae*. *Plasmodium falciparum* is more common in sub Saharan Africa and Melanesia (Papua New Guinea, Solomon Islands) than elsewhere and it is the deadliest as it also causes severe forms of the disease. It is the dominant species in Africa, which helps to explain the region's high death rate attributable to malaria; *Plasmodium vivax* is common in Central and South America, India, N. Africa and Middle East; *Plasmodium ovale* is common in Western Africa and *Plasmodium malariae* is sporadic worldwide.

#### 1.1 Global malaria burden

At present about 100 countries in the world are considered malarious, almost half of which are in Africa, south of Sahara. More than 2400 million of the world's population (40%) is at risk. The incidence of malaria worldwide is estimated to be 300–500 million clinical cases each year, with about 90% of these cases occurring in Africa, south of Sahara mostly caused by *Plasmodium falciparum*<sup>1</sup>.

#### 1.2 Malaria burden in Africa

Malaria is Africa's leading cause of under-five mortality (20%), killing 200-500 children every one hour. Anaemia, low birth-weight and neurological problems are the frequent consequences of malaria, compromising the health and development of millions of children throughout the tropical world. Over 40% of the world's children live in malaria-endemic

countries. Of the approximately 300 to 500 million malaria infections and of over one million deaths each year, 75% occur in African children aged less than 5 years infected with *Plasmodium falciparum*<sup>2</sup>.

### 1.3 Malaria burden in Tanzania

Malaria is endemic across nearly all of mainland Tanzania in which 93% of the population lives in areas where *Plasmodium falciparum* is transmitted. Prevalence of malaria among children aged less than 5 years ranges from 0.4% in the elevated region of Arusha to 41.1% in the northwestern region of Kagera (Figure 1 of Appendix 4). Unstable seasonal malaria transmission occurs in approximately 20% of the country, while stable malaria with seasonal variation occurs in another 20%. The remaining malaria endemic areas in Tanzania (60%) are characterized as stable perennial transmission. The majority of malaria in Tanzania is caused by the malaria parasite *Plasmodium falciparum* and the principal vector is *Anopheles gambiae*.

Tanzania has unacceptably high burden of morbidity and mortality caused by malaria. Every year, 14–18 million new malaria cases are reported in Tanzania, resulting in 120,000 deaths. Of these deaths, 70,000 are in children less than five years of age. Malaria is the leading cause of outpatients, inpatients, and admissions of children less than five years of age at health facilities<sup>3</sup>.

Although there are effective management, and control strategies that can mitigate this burden, many challenges still remain that impede effective mitigation efforts. There is therefore a need to revisit national implementation strategies for malaria interventions.

Malaria is the number one killer among children in Tanzania, and mothers who contract malaria during pregnancy run the risk of having low birth weight babies, maternal anemia, impaired fetal growth, spontaneous abortions, stillbirths and premature babies.

Growing resistance to first-line antimalarial drugs in recent years has greatly diminished the government's ability to treat the disease<sup>4</sup>.



Key among the factors contributing to the increasing malaria mortality and morbidity is the widespread resistance of *Plasmodium falciparum* to conventional antimalarial drugs, such as chloroquine, sulfadoxine–pyrimethamine (SP) and amodiaquine.

Resistance to inexpensive antimalarials such as chloroquine and SP has developed or is developing rapidly, with increased mortality as a result. Tanzania, like many countries in the region, has reported chloroquine and some sulfadoxine-pyrimethamine (SP) resistance to *Plasmodium falciparum*<sup>5</sup> and Alu, an artemisinin-based combination therapy (ACT) is currently recommended as the first line drug in their national antimalarial treatment policy for uncomplicated malaria<sup>1</sup>.

#### **1.4 Roll back malaria and role of chemotherapy**

Recognition of the unacceptable high mortality and morbidity from malaria in Africa, and the availability of a number of evidence based, cost-effective interventions, led to the formation, in 1998, of the Roll Back Malaria initiative. In the Abuja Declaration of April 2000, African Heads of State resolved to support scaling-up of the following interventions, which, if brought to effect in malaria-endemic countries, could have a significant impact on both morbidity and mortality from malaria. The interventions form the core of the Roll Back Malaria strategy, aimed at halving mortality from malaria in Africa by 2010. The National Malaria Medium-Term Strategic Plan was developed to strengthen previous initiatives aimed at reducing malaria morbidity and mortality in the country by 25 % by 2007 and by 50 % by 2010 in line with the RBM goals.

Four strategic approaches were adopted in order to meet the objectives, and these include improved malaria case management through early diagnosis and prompt treatment, vector control through the universal use of insecticide-treated nets (ITNs), control of malaria in pregnancy, malaria epidemic prevention and control.

Additionally, there are three supportive and complementary strategies. These are operational research, communication and monitoring and evaluation.



The combination of tools and methods to combat malaria now includes long-lasting insecticidal nets (LLIN) and artemisinin-based combination therapy (ACT), supported by indoor residual spraying of insecticide (IRS) and intermittent preventive treatment in pregnancy (IPT)<sup>6</sup>.

Disease management remains a fundamental and indispensable element of malaria control. Its aims are prompt and adequate treatment of suspected/ confirmed cases, to avoid the progression of mild malarial disease to severe or complicated disease, to prevent death or sequelae from severe and complicated malaria, to prevent transmission of malaria in certain situations and to minimise the risk of selection and spread of drug resistant parasites.

The inappropriate use of antimalarial drugs during the past century has contributed to the current situation of widespread resistance and the associated disease burden; antimalarial drugs were deployed on a large scale, always as monotherapies. A significant rise in malaria mortality in children under 5 years of age has been observed in Senegal in West Africa, coinciding with the emergence of chloroquine resistance in the area<sup>7</sup>. The incidence of severe malaria has risen with increasing chloroquine resistance in Malawi and Democratic Republic of the Congo<sup>8</sup>. Antimalarial drug resistance has also been implicated in the increasing frequency and severity of epidemics<sup>9</sup>.

### **Antimalarial drug resistance**

Antimalarial drug resistance that has spread and intensified over the last 15-20 years has led to a dramatic decline in the efficacy of the most affordable antimalarial drugs. As a response to increasing levels of resistance to antimalarial medicines, WHO recommended that all countries experiencing resistance to conventional monotherapies, such as chloroquine, amodiaquine or sulfadoxine-pyrimethamine, should use combination therapies, preferably those containing artemisinin derivatives (ACTs – artemisinin-based combination therapies) for falciparum malaria<sup>10,11</sup>. It has also lowered the resistance-threshold recommended for

treatment policy change from 25% to 10% as assessed by standard WHO protocols in children under 5 years of age<sup>12</sup> meaning that a more effective treatment should be adopted when the proportion of treatment failures to the old treatment reaches 10%. It currently recommends the following combination therapies; artemether/lumefantrine; artesunate plus amodiaquine in areas where the cure rate of amodiaquine monotherapy is greater than 80%; artesunate plus mefloquine; and artesunate plus sulfadoxine/pyrimethamine in areas where the cure rate of sulfadoxine/pyrimethamine is greater than 80%.

Tanzania, has reported chloroquine and sulfadoxine-pyrimethamine (SP) resistance to *Plasmodium falciparum* and Alu, the artemisinin-based combination therapy (ACT) is currently recommended as the first line drug in the national antimalarial treatment policy for uncomplicated malaria<sup>1</sup>.

In many malarious areas, a majority of the population does not have ready access to antimalarial drugs and to reliable and consistent information about malaria treatment and prevention<sup>13</sup>.

Moreover, those drugs that are available are frequently obtained from informal sources and may be counterfeit; they are of variable quality, may be partially or completely ineffective against local parasite strains, and are often used in inappropriate dosages<sup>13</sup>.

#### **Artemisinin based combination therapy**

Over the past decade, a new group of antimalarials, the artemisinin compounds, especially artesunate, artemether and dihydroartemisinin have been deployed on an increasingly large scale. Artemisinin compounds, used in combination with a longer acting antimalarial, can rapidly reduce parasite densities to very low levels at a time when drug levels of the longer acting antimalarial are still maximal. This greatly reduces both the likelihood of parasites surviving initial treatment and the likelihood that parasites will be exposed to suboptimal levels of the longer acting drug<sup>14</sup>. Second, the use of artemisinins has been shown to reduce

gametocytogenesis by 8- to 18-fold<sup>10</sup>. This reduces the likelihood that gametocytes carrying resistance genes are passed onwards and potentially may reduce malaria transmission rates.

Artemisinin has a very different mode of action which makes it particularly useful in the treatment of resistant infections. At present there is no known resistance to artemisinin and very few reported side-effects to drug usage. If used alone, the artemisinins will cure *falciparum malaria* in 7 days, but studies have shown that in combination with certain synthetic drugs they produce high cure rates in 3 days with higher adherence to treatment<sup>15</sup>. Combination therapy offers hope for preserving the efficacy of antimalarial drugs and prolonging their useful therapeutic life<sup>16-18</sup>. The development of artemisinin and its derivatives, the most rapidly acting of all the current antimalarial drugs, and recognition of their potential role as a component of combination therapy<sup>10,14,17,18</sup>, have led to several large trials aimed at assessing different combinations of existing drugs, and to the specific development of new combination drugs.

### **Malaria treatment guidelines and barriers to successful case management**

National malaria treatment guidelines are essential for providing countries with a framework for the safe and effective treatment of uncomplicated and severe malaria as well as for the prevention of malaria in vulnerable groups, such as pregnant women and young children. Such policies aim at the reduction of malaria mortality and morbidity, contain the development of resistance. All health care providers in both the public and private health sectors are expected to be aware of, understand the rationale for, and implement the national malaria treatment guidelines.

To provide adequate early diagnosis and treatment (EDT) at the primary healthcare level is one of the aims of the Roll Back Malaria strategy. EDT provides secondary prevention and halts progress of the disease process to incurable stages. An important threat to this strategy is poor diagnosis.



Presumptive treatment as a strategy for malaria management is common in most rural health facilities in Tanzania where laboratory facilities are inadequate. While its potential benefits are clear in high transmission settings, they are questionable in areas with low malaria transmission. Various studies in Tanzania have not been able to show whether or how the level of endemicity affects the sensitivity and specificity of clinical malaria case definition<sup>19</sup> and rationale of presumptive treatment. In one study, the fraction of malaria-attributable fevers in health facilities in Dar es Salaam was low, suggesting that patients presenting with fever are much more prone to suffer from febrile diseases other than malaria<sup>20</sup>.

It has been reported that 87% of patients who received antimalarial treatment at the Muhimbili National Hospital in Tanzania for presumed severe malaria did not have detectable parasitaemia resulting in overtreatment of malaria and neglecting other potentially threatening conditions<sup>21</sup>. Recently, in northeastern Tanzania it has been observed that 53.9% of patients treated for malaria were smear-negative for *Plasmodium falciparum*.<sup>22</sup> This has important implications for the management of febrile illnesses, in which, bacterial illnesses requiring antibiotics may be missed<sup>23</sup>. It poses a problem of increased drug pressure and drug resistance and misdiagnosing malaria patients distracts health care providers from other causes of fever, some of which may be fatal. This may lead to a substantial number of unnecessary treatments, a problem that is likely to be much more serious with the introduction of the more expensive artemisinin-based combination therapy<sup>24</sup>.

Moreover, there are in some settings where those in need of antimalarials may not receive them, for instance, some children who access care in the health sector may not be prescribed with antimalarials appropriately or may not receive them at all. For example, in Zambia after policy change, Alu was available in 51% of health care facility, but only 22% of children who needed Alu received AL<sup>25</sup>.

Another major barrier to the successful malaria case management is the preference and adherence to drug regimens. If it is perceived that health workers treat most patients rudely,

that they do not have the appropriate drugs, or that the general quality of their services is inadequate, this will also influence a first preference for home treatment<sup>26</sup>. Preference and adherence to drug regimens is also a function of age and sex of the child. For example in a study of malaria treatment in Malawi, researchers found that clinic attendance was positively correlated with young age of the child, defined in this study as less than four years and that male children were more likely to receive the correct dosage of antimalarial drug than were females<sup>27</sup>.

Underdosing is quite a common practice in many households because of poverty and the fact that clinical cure of fever is what matters to many individuals. In Sri Lanka, antimalarial tablets circulated freely within the village, they were passed around according to need and that keeping a few tablets in stock was important, just in case somebody got sick or developed fever<sup>28</sup>. This behaviour may be one of the reasons for drug resistance. Improper or inappropriate use of anti-malarial drugs is the result of a number of factors. Illiteracy may be a significant issue: people who are unable to read the instructions on or in the medicine packages may not understand the correct dosage<sup>29</sup>. If health workers do not correctly explain how to use drugs, if the health workers themselves are misinformed, or if the medicine is bought at a shop where incorrect or little information is given, the potential for misuse is high<sup>30</sup>. Underdosing in circumstances like this is the most common result. It is well known that mutant parasites are selected if antimalarial drug concentrations are sufficient to inhibit multiplication of susceptible parasites but are inadequate to inhibit the mutants, a phenomenon known as drug selection<sup>31</sup>. This selection is thought to be enhanced by sub therapeutic plasma drug levels and by a flat dose-response curve to the drug. Drug resistance necessitates the use of drugs which are more expensive. The problem of drug resistance can be attributed primarily to increased selection pressures on *P. falciparum* in particular, due to indiscriminate and incomplete drug use for self treatment.

Moreover, those drugs that are available are frequently obtained from informal sources and may be counterfeit; they are of variable quality, may be partially or completely ineffective



against local parasite strains, and are often used in inappropriate dosages<sup>13</sup>. Although a range of anti-malarials is available in the market, the fact that many of those who self-treat purchase their drugs from poorly-informed shopkeepers and drug sellers is a significant reason for concern about misinformation on appropriate treatment<sup>32</sup>.

In a study in Ethiopia, reasons for failing to complete a full course of treatment included unpleasant taste of the drug and subsidence of malaria symptoms, which made further use of the drug unnecessary<sup>26</sup>.

Perceptions about the cause and appropriate methods to be used can play a large role in the type of treatment chosen. In Tanzania, researchers found that local residents made use of treatment methods based upon different types of patients (male, female, pregnant female, young child) and different presentations of the disease<sup>33</sup>. In a more serious and potentially deadly example, other researchers in Kenya reported that convulsions ( indication severe cerebral malaria), considered life-threatening, were attributed to supernatural causes and anti-malarial drugs and anti-pyretics were counterindicated when convulsions occurred, and were actually withheld or withdrawn from children having convulsions<sup>34</sup>. Moreover, the type of treatment used for convulsions at hospital is not consistent with traditional expectations; reason enough for mothers to avoid taking children with these symptoms to hospitals. Injections are the primary form of treatment in these instances, but it is these procedures that are believed by mothers to cause the death of children with convulsions at hospital. Perhaps most paediatric malaria deaths occur in hospital emergency wards because that is where children are brought when their illness is often too far advanced to respond to treatment. Unfortunately, these deaths only serve to reinforce the idea that children with convulsions who are brought to health clinics do not survive the treatment<sup>35</sup>.

Self-treatment, both with anti-malarial drugs and traditional remedies, was higher in rural areas due to differential access to health facilities, income levels, educational level, and prevalence of the disease. Concern over cost of treatment is a primary reason for non-use of

health clinics, as well as being a primary motivator for self-treatment, the main problem being ability, not willingness, to pay<sup>36</sup>.

Visits to health centres, entail additional and sometimes prohibitive costs, including travelling expenses and time lost from productive activities. Since malaria is a major problem in rural areas, the remote location of many villages can serve as a barrier to treatment. Similarly, in a study of malaria treatment practices among mothers in Guinea, researchers found that rural mothers who lived farthest from health facilities were less likely to attend to these health facilities and were more late in administering medication to sick children than women who lived closer to health clinics<sup>37</sup>. Timely delivery of supplies, preventing drug pilfering along the supply route and ensuring that most drugs reach their intended destinations and preventing deterioration of the drugs during transport can be formidable<sup>36</sup>. In a study of childhood treatment of malaria along the Kenyan Coast, researchers found that 55% of mothers who were given medication for their children did not understand instructions and did not ask clinic staff for verification. The reason they gave for their failure to make inquiries was that health-centre staff could be harsh and rude when asked too many questions<sup>35</sup>.

## **1.5 Malaria case management in children aged less than 5 years**

### **1.5.1 Symptom recognition and care seeking**

To reduce mortality will require greater emphasis on recognizing symptoms at home; prompt care-seeking, improved quality of care at health facilities and better adherence to treatment<sup>38</sup>.

There have been a number of studies of care-seeking for malaria in Africa reviewed by McCombie in 1996<sup>39</sup> and updated in 2002<sup>40</sup> with much additional work since then<sup>41,42</sup>. Almost every study identified local community perceptions, terminology or explanations of illness that overlap with malaria disease in ways that distinguished fever, malaria and convulsions as distinct in aetiology and required treatment. Care-seeking patterns for simple fever or uncomplicated malaria were more likely managed initially at home while cases with convulsions or severe malaria were more likely to seek care from a health care practitioner. Multiple care seeking events and switching between types of providers were common. Cases with simple fever or uncomplicated malaria were more likely to seek formal, modern



biomedical care and antimalarial drugs, while cases with convulsions were more likely to be managed by traditional healers or traditional practices, as well as modern care. The hierarchy of such events is likely to affect timely access to effective care. Communities' recognition and awareness of major symptoms of malaria in children could encourage action, but perceptions of their causes and poor discrimination of other danger signs such as vomiting and failure to feed, might impede early treatment<sup>43</sup>.

Attention to these perceptions is critical to public health efforts. For example, beliefs that differ from the scientific explanation about the cause and transmission of malaria may lead to inaction, a delay in seeking appropriate treatment, or ineffective action, all with serious consequences. Fevers and other severe and unstable varieties of symptoms, such as convulsions, are frequently not associated with malaria, obviating the need for treatment or preventive measures associated with these symptoms, which can have dire consequences for the sufferer<sup>44-45</sup>. In Tanzania, a study confirmed that the population refers to the signs and symptoms associated with the biomedical condition of malaria as three distinct conditions, each with its own aetiology, treatment-seeking patterns and prognosis. The three conditions are: "homa" (fever, vomiting, feeling cold, loss of appetite, limp body, red eyes, not considered life threatening); "malaria" (high fever, vomiting, loss of appetite, feeling cold, some caretakers considered life threatening) and "degedege" (high fever, loss of appetite, stiffness of body, rolling of eyes, lips twisted sideways, twitching, considered life threatening). Anaemia is not often recognized, and where recognized, is not associated with malaria. For example, severe and life threatening anaemia, likely to be due to malaria, is prevalent in young children over six months of age in one study area in Tanzania<sup>46</sup> yet deaths due to anaemia with malaria are recorded infrequently. These are well recognized by most households in the study population. Although "homa" and especially "malaria" were seen as associated with malaria and mosquitoes, in most cases the signs and symptoms of "degedege" are not attributed to malaria. Homa" and "malaria" are seen as conditions that can be managed at least initially at home with modern medicine available from shops and from health facilities<sup>38</sup>.

Home treatment include the use of modern medicines, such as paracetamol from local shops, in the early stages the illness. If the illness reaches a severe stage (convulsions) people claim to use traditional healers in the home or outside the home. Biomedical care ranging across government hospitals, health centres, dispensaries and equivalent private facilities was used in the later stage. In the multiple-care-seeking group, switching between modern care and traditional care can be a factor in the delay of effective care<sup>38</sup>.

Knowledge of appropriate treatment regimens is lacking on the part of the public as well as on the part of private providers<sup>47, 48</sup>. Malaria is perceived by caregivers as a mild disease, and if it becomes serious or life threatening, then, the perceived diagnosis changes from malaria to something that is more likely to be treated with traditional medicine or practices. These beliefs are not rigid. Every case is subject to a process of continuing debate and re-evaluation such that modern pharmaceuticals are also sought, albeit with delay, when convulsions fail to resolve or reoccur after traditional medicine<sup>49</sup>.

Care seeking patterns in 2000s, has improved compared to 1980s in terms of accessibility, drug availability and peoples attitude towards modern health care utilization with inclination towards modern care. This has followed government providers securing adequate, subsidized drug supplies under the health reforms and offering the integrated management of childhood illness (IMCI) strategy. For example, in one of malaria studies in Bagamoyo, government providers were the choice in only 45% of the subjects<sup>50</sup> while in recent similar study in Rufiji, modern health care was the choice in 78.7% of the subjects<sup>38</sup>. But despite high rates of modern care seeking for all forms of malaria, and despite relatively high attendance and utilization of modern care as seen in Tanzania, malaria mortality remains high. There could be factors related to the clients, the health care providers, quality of modern care and patient adherence to treatment regimens once obtained of which this study aimed to examine.

### **1.5.2 Disease diagnosis**

Malaria is diagnosed by clinical symptoms and microscopic examination of blood. The common symptoms and signs of uncomplicated malaria for children under 5 years of age are



fever (raised temperature detected by thermometer or touch) or a history of fever, loss of appetite, weakness, pallor, enlarged spleen, vomiting and diarrhea.

Most of these symptoms appear around 9 -14 days after the initial mosquito bite. The time differs according to the species of *Plasmodium*.

Malaria may lead to anemia and jaundice because the red blood cells are destroyed faster than they can be replaced. Severe anemia is the leading cause of death in children with malaria.

Diagnosis should be supported microscopically by the identification of the parasites on a thin or thick blood smear. The only rare exception is *P. falciparum*, in which all the parasites during the life cycle can be sequestered out of the peripheral blood in late-stage forms. Advantages of microscopic diagnosis include differentiation between species, quantification of the parasite density and ability to distinguish clinically important asexual parasite stages from gametocytes which may persist without causing symptoms. These advantages can be critical for proper case-management and evaluating parasitological response to treatment. Specific disadvantages are that slide collection, staining, and reading can be time-consuming and microscopists need to be trained and supervised to ensure consistent reliability.

### **Presumptive Diagnosis**

In highly endemic areas particularly in Africa, the great prevalence of asymptomatic infections and lack of resources such as microscopes and trained microscopists have led peripheral health facilities to use presumptive treatment. Patients who suffer from a fever that does not have any obvious cause are presumed to have malaria and are treated for that disease, based only on clinical suspicion, and without the benefit of laboratory confirmation.

Clinical diagnosis offers the advantages of ease, speed, and low cost and allows the treatment of a potentially fatal disease. But it also leads frequently to incorrect diagnoses and to misdiagnose many who do not have malaria<sup>51</sup> and consequently unnecessary use of antimalarial drugs<sup>52</sup>. This results in additional expenses and increases the risk of selecting drug-resistant parasites. Considerable overlap exists between the signs and symptoms of malaria and other frequent diseases, especially acute lower respiratory tract infection (ALRI),



and can greatly increase the frequency of misdiagnosis and mistreatment<sup>53</sup>. Attempts to improve the specificity of clinical diagnosis for malaria by including signs and symptoms other than fever or history of fever have met with only minimal success<sup>54</sup>.

### 1.5.3 Antimalarial drugs

Disease management remains a fundamental and indispensable element of malaria control. Its aims are prompt and adequate treatment of suspected/ confirmed cases, to avoid the progression of mild malarial disease to severe or complicated disease, to prevent death or sequelae from severe and complicated malaria, to prevent transmission of malaria in certain situations, and minimise the risk of selection and spread of drug resistant parasites.

#### Chloroquine

Chloroquine is a 4-aminoquinoline that has marked and rapid schizonticidal activity against all infections of *P. malariae* and *P. ovale* and against chloroquine-sensitive infections of *P. falciparum* and *P. vivax*. It is also gametocytocidal against *P. vivax*, *P. malariae* and *P. ovale* as well as immature gametocytes (stages 1-3) of *P. falciparum*. It mildly suppresses the immune system. It is used in some autoimmune disorders, such as rheumatoid arthritis and lupus erythematosus. It also has antipyretic and anti-inflammatory effects.

It is extremely safe, has few side effects and is low in cost. Resistance has restricted its effectiveness as most strains of *P. falciparum* are resistant to chloroquine and cases of *P. vivax*-resistant malaria have also been detected. In Africa, chloroquine resistance was first documented in the United Republic of Tanzania in 1979 and has spread and intensified in the last 20 years. In most countries of East Africa and in Ethiopia more than 50% of patients currently experience a recurrence of parasitaemia with symptoms by day 14 after treatment. Moderate levels of resistance are found in central and southern Africa. In West Africa, reported rates of resistance vary widely but tend to be lower than in central and southern Africa. Strains of *P. falciparum* remain sensitive to chloroquine in Central America north of

the Panama Canal, the island of Hispaniola (Haiti and the Dominican Republic) and in El Faiyûm governorate in Egypt.

### **Antifolate drugs**

The only useful combinations of antifolate drugs for the treatment of malaria are synergistic mixtures that act against the parasite-specific enzymes, dihydropteroate synthetase and dihydrofolate reductase. Available combinations include the sulfa drug-pyrimethamine combinations sulfadoxine-pyrimethamine and sulfalene-pyrimethamine. Sulfa drug-pyrimethamine combinations are highly active blood schizonticides against *P. falciparum* but do not have gamete-toctocidal activity. The long half-life of sulfa drug-pyrimethamine combinations provides a potent selective pressure for parasite resistance in areas of high transmission. In Africa since the late 1980s, *P. falciparum* sensitivity has decreased, particularly in East Africa where sulfadoxine-pyrimethamine has been used on a large scale<sup>55</sup>. Sulfa drug-pyrimethamine combinations have been successfully used in areas with highly developed *P. falciparum* resistance to chloroquine and during malaria epidemics. Compliance is high since they offer single-dose therapy. There is evidence that folic acid, even in physiological doses, administered concurrently with sulfadoxine-pyrimethamine, can antagonize the action of sulfadoxine<sup>56</sup>. It has been suggested that folic acid supplements should be delayed for one week after sulfa drug-pyrimethamine treatment to avoid an inhibitory effect on antimalarial efficacy.

Sulfa drug-pyrimethamine combinations are generally well tolerated when used at the recommended doses for malaria therapy. The most serious events are associated with hypersensitivity to the sulfa component, involving the skin and mucous membranes and normally occurring after repeated administration. High levels of resistance to SP are found in the Amazon Basin and throughout South-East Asia, with the possible exception of some areas in eastern Cambodia and northern Viet Nam. In Tanzania, resistance to SP has been reported to be on increase. Recent studies in Tanzania indicate that the mean SP failure rate is now at 25.5%<sup>57</sup>.

### **Quinine**

This drug comes from the bark of the Cinchona tree. Quinine is normally effective against falciparum infections that are resistant to chloroquine and sulfa drug-pyrimethamine combinations. Decreasing sensitivity to quinine has been detected in areas of South-East Asia where it has been extensively used for malaria therapy. This has occurred particularly when therapy was given in an unsupervised settings with regimens longer than 3 days. In these settings, patient adherence to therapy is low, leading to incomplete treatment; this may have led to the selection of resistant parasites. Strains of *P. falciparum* from Africa are generally highly sensitive to quinine. Quinine is still the drug of choice for severe falciparum malaria in most countries. Cinchonism, a symptom complex characterized by tinnitus, hearing impairment, and sometimes vertigo or dizziness, occurs in a high proportion of treated patients. Hypoglycaemia may be caused by quinine since the drug stimulates secretion of insulin from pancreatic beta-cells.

### **Artemisinin and its derivatives**

Artemisinin (*qinghaosu*) is an antimalarial isolated by Chinese scientists from the plant *Artemisia annua* L. It is a sesquiterpene lactone with a peroxide bridge linkage. Artemisinin is poorly soluble in oils or water but the parent compound has yielded dihydroartemisinin, the oil-soluble derivatives artemether and arteether, and the more water-soluble derivatives sodium artesunate and artelinic acid. These derivatives have more potent blood schizonticidal activity than the parent compound and are the most rapidly effective antimalarial drugs known. They are used for the treatment of severe and uncomplicated malaria. They are not hypnozoiticidal but gametocytocidal activity has been observed<sup>10</sup>. Artemisinin and its derivatives are effective for both treating the disease and reducing its transmission by acting rapidly on the parasites, destroying the asexual forms and gametocytes present in the blood. The antimalarial activity of artemisinin and its derivatives is extremely rapid and most patients show clinical improvement within 1-3 days after treatment. However, the recrudescence rate is high when the drugs are used in monotherapy, depending on the drug dose administered, the duration of treatment and the severity of disease, but not at present on parasite resistance<sup>59</sup>.



Treatment for less than 7 days gave unacceptably high recrudescence rates<sup>60</sup>. So far there is no confirmed evidence of resistance of *P. falciparum* to artemisinin and its derivatives. To reduce the recrudescence rate and the risk of development of resistance, as well as to improve compliance, artemisinin should preferably be administered in combination with another effective blood schizonticide.

### **Combination therapy**

This is the combined use of two or more drugs that have differing modes of action and act on differing sites on the parasite. Combinations of anti malarial drugs need to be given singly at the same time or formulated into a single tablet/injection. Using combination of drugs reduces the possibility of *Plasmodium* developing resistance and it also improves treatment efficacy. Results from field trials show that combining antimalarial drugs such as SP, to which resistance is developing rapidly, with artesunate, an artemisinin derivative, improves cure rates for malaria<sup>61-63</sup>.

Artesiminin based combination has potential advantages in that they are highly efficacious with rapid clearance of parasites.

They have potential to delay or slow development of drug resistance, they lead to decrease in gametocyte carriage which in turn leads to decrease in transmission. They are generally safe and well-tolerated.

#### **1.5.4 Treatment of uncomplicated malaria using artemether-lumefantrine (Alu)**

The management of malaria disease in children includes recognition of symptoms of the patient by the caregiver, diagnosis of malaria disease and/ or other febrile conditions by the health care provider, prescription and dispensing of the correct drugs of assured quality by the health care providers, with the first dose always being taken under supervision; compliance by the caregiver with prescription instructions; follow-up to check whether the expected therapeutic efficacy has been achieved, education of patient or family on how to take or



administer the drugs, when to return to health facility, danger signs, and prevention of malaria<sup>64</sup>.

The introduction of pre-packaged doses of ACTs has been shown to be effective in improving provider and client adherence<sup>65,66</sup>.

Operational research findings have shown that appropriate packaging and labelling improves compliance, enhances acceptability<sup>67,68</sup> and greatly reduces the risk of overdosing<sup>69</sup>. Adherence to prepackaged tablets is much better than to syrup; and the cost of prepackaged treatments is much lower<sup>70</sup>. Training health facility workers and equipping them with packaged treatments have been shown to reduce case fatality rates<sup>71</sup>. Prepackaging of drugs for specific age and weight ranges<sup>70</sup> also improves home management of malaria.

### **Artemether-lumefantrine**

Artemether-lumefantrine is a new, oral, fixed-dose combination of artemether, an artemisinin derivative, and lumefantrine. This combination provides a higher rate of antimalarial effectiveness than when the individual components are used as monotherapies. Artemether, produces rapid schizontocidal effects, resulting in prompt fever reduction and parasite clearance<sup>61</sup>. Recrudescence rates are high unless treatment is continued for at least 5–7 days, which increases the likelihood of compliance problems. Lumefantrine has a much longer half-life and does not produce a high cure rate until several days of therapy have been given. Clinical and parasitologic response is much slower when compared with artemether. Used together, the artemether-lumefantrine combination produces both rapid antimalarial efficacy and low recrudescence rates.

First, artemisinin compounds, used in combination with a longer acting antimalarial, rapidly reduce parasite densities to very low levels at a time when drug levels of the longer acting antimalarial drug are still maximal. This greatly reduces both the likelihood of parasites surviving initial treatment and the likelihood that parasites will be exposed to suboptimal levels of the longer acting drug<sup>14</sup>. Second, the use of artemisinins has been shown to reduce

gametocytogenesis by 8- to 18-fold. This reduces the likelihood that gametocytes carrying resistance genes are passed onwards and potentially may reduce malaria transmission rates.

The artemether-lumefantrine combination is in a single-tablet dosage form, with each tablet containing 20 mg of artemether and 120 mg of lumefantrine. The product is usually given for only three days, a feature that may foster patient compliance with therapy<sup>72</sup>. More importantly, artemether and lumefantrine act synergistically *in vitro* against *P. falciparum*, which theoretically reduces the risk of resistance developing to either compound<sup>62</sup>. The single-tablet formulation prevents patients from taking either drug component alone, further averting resistance problems. Neither clinical nor *in vitro* resistance to artemisinin compounds has yet been reported, despite widespread use in places such as China and Vietnam<sup>73</sup>.

Clinical studies conducted in China, The Gambia, Tanzania, Thailand, and India have already proven artemether-lumefantrine to be highly effective against multidrug-resistant strains of malaria, and well tolerated in adults and children<sup>61-63</sup>.

### **Challenges to the use of artemether-lumefantrine**

Introduction of artemisinin-based combination therapy (ACT) is one of the challenges facing Tanzania. Tanzania introduced ACTs in November 2006. One key issue is the cost of ACTs, which are 20 times higher than the cost of conventional therapies (TSH12000-15000 in private pharmacies and drug shops). The monthly income in one study in a rural area in Tanzania was Tanzanian shillings 150000<sup>74</sup>. This finding shows that the amount spent on malaria treatment is 10% of the total household income. Major limitations in adoption and implementation of ACTs reported by Bloland and others<sup>75</sup> were high costs, high malaria transmission rates, inappropriate use of drugs, inadequate diagnostic facilities, ill-informed policy makers and weak public health systems in Africa. Other issues include shortages of artemether-lumefantrine in public health facilities because of the high demand and limited supply.

Acceptability and adherence to treatment by patients are major components in the success of any public health system and are influenced by both behavioural and economic factors. They

are determined by duration of treatment, number of daily doses, speed of clinical response particularly the antipyretic effect, minor adverse effects, market-price relative to household economy or affordability, presentation, packaging, health education, taste and/or colour, and size of tablet (or volume per dose for syrups and suspensions) and reputation of the drug. Simple technology, like blister packaging of antimalarial drugs, may offer some solutions to the problem of incorrect use<sup>76</sup>.

Another concern about artemisinin based combination therapy is the extent to which the components might be used as monotherapies outside official health services. Already, artemisinin compounds are available in the pharmacies. As supply increases and the price drops, these drugs will be used increasingly for the treatment of fever and, because of the rapidity of action, they may in fact become the community's drug of choice. Any benefits of combination therapy in preventing development or intensification of resistance may be lost due to unofficial and incorrect use of the component drugs outside of official health services. Although WHO has strongly recommended the abandonment of artemisinin monotherapy, regrettably, many of these compounds are still being sold. Gelband and Seiter<sup>77</sup> state that the ACTs were identified as needing immediate support and an appropriate use of ACTs would delay the emergence of parasite resistance to artemisinin monotherapy, which has been marketed actively by several companies.



## CHAPTER 2

### 2.0 PROBLEM STATEMENT AND STUDY JUSTIFICATION

Despite high rates of modern care-seeking for all forms of malaria, and despite relatively high attendance and utilization of modern care as seen in Tanzania, malaria mortality remains high. There could be factors related to the clients, the health care providers, quality of modern care in terms of disease diagnosis, prescription and dispensing of drugs in correct dosages and time schedules of which this study aimed to examine.

Reduction of malaria related mortality and morbidity require caregivers' knowledge on recognizing symptoms at home, prompt care-seeking, improved quality of care at health facilities and better adherence to treatment<sup>38</sup>. For example a study by Tarimo<sup>78</sup> showed that when a sick child gets febrile convulsions as might happen in the case of uncomplicated malaria, caregivers would initially seek traditional remedies that would delay modern care seeking for treatment with Alu.

Tanzania has amended the malaria treatment policy twice, the first amendment being in August 2001 when SP replaced chloroquine and the second being in January 2007 when artemether-lumefantrine (Alu) replaced SP for the treatment of uncomplicated malaria. The goal of the amendments was to reduce morbidity, mortality and economic losses and to encourage rational drug use in order to minimize the development of drug resistance. Resistance can develop if artemisinin combination therapies (ACTs) are used unjudiciously as in presumptive diagnosis and treatment of malaria, which is the case in many health care facilities. There are very few reports on the quality of clinical practices following implementation of Alu policies in Africa in general and Tanzania in particular. Furthermore, it is not known what percentage of children suffering from uncomplicated malaria receive ACTs on clinical grounds while in fact they have or have no malaria as confirmed by laboratory diagnosis.



The use of antimalarial drugs in combination therapy is fairly a new concept. It has previously been shown that, health workers have a tendency of advising patients to continue using antimalarial drugs familiar to them<sup>25</sup>. It is not known whether health care workers will adhere to the use of Alu as first line treatment or will continue using other antimalarials. For example according to WHO Malaria Report 2008, in most African countries, 38% of children with fever were treated with antimalarial drugs, but only 3% with ACTs<sup>6</sup>. There are settings where those in need of antimalarials, are not prescribed with antimalarials appropriately<sup>25</sup>.

These premises suggest that research aimed at examining how recognition of symptoms is made at home and how prompt and appropriate treatment using the quality and efficacious antimalarial available is made at the health care facility as well as the compliance with the full course of treatment; is needed.

## CHAPTER 3

### 3.0 RESEARCH QUESTIONS AND OBJECTIVES

#### 3.1 General research questions

1. What are the current practices for malaria case management in underfives after the introduction of Alu as the first line treatment of uncomplicated malaria?
2. How do the practices compare with the national and IMCI guidelines and how does this affect malaria case management?
3. What are the factors affecting prompt and effective malaria case management in underfives in the era of Alu?

#### 3.2 Specific research questions

1. How is malaria illness in children under 5 years of age recognized by the caregiver?
2. How does this recognition comply with the national treatment and IMCI guidelines and how does this affect prompt and effective case management?
3. What proportion of children with symptoms and signs of malaria have laboratory-confirmed malarial disease and therefore warrant Alu taking?
4. What are the factors which affect the prescribing of Alu by the health care providers?
5. What do caregivers know about the correct use of artemether-lumefantrine under directly observed therapy and subsequent administration at home?

### 3.3 Broad objective

To determine the current practices for childhood malaria case management using artemether-lumefantrine for uncomplicated malaria in settings without microscopy facilities in Kisarawe and Kibaha Districts, Tanzania.

### 3.4 Specific objectives

1. To assess the proportion of children with uncomplicated malaria who are appropriately managed according to national and IMCI guidelines.
2. To determine the proportion of children with clinically diagnosed malaria who have laboratory confirmed diagnosis.
3. To assess proportion of caregivers with appropriate knowledge on symptoms of malaria illness in the sick child
4. To assess proportion of caregivers with appropriate knowledge on the correct use of artemether-lumefantrine under directly observed therapy and subsequent administration at home.
5. To examine the relationship of selected sociodemographic factors with the above four variables

## CHAPTER 4

### 4.0 METHODOLOGY

#### 4.1 The survey setting

Tanzania is located in East Africa, covering an area of 945000 km<sup>2</sup>. The country is divided into 25 and 121 administrative regions and districts respectively. The climate of the country varies with geographical zones. It is tropical type on the coast, where it is hot and humid with rainy season between March and May; semi-temperate type in the mountains with the short rains (*vuli*) between November and December and the long rains (*masika*) between February and May and dry (*kiangazi*) in the plateau region with considerable seasonal variations in temperature. Total rainfall increases towards the North around Lake Victoria. Rainfall is well distributed throughout the year reaching peak during the period of March and May. The average temperature is between 20°C and 32°C. Average annual rainfall approximately ranges from 600mm to 1,800 mm per year under normal conditions and depending on the elevation of a place from sea level. The average duration of the dry season is 5 to 6 months.

The population of Tanzania constitutes the very large number of persons at risk for malaria. Approximately 40 million individuals of which 38.6 million persons in the Mainland and 1.3 million persons in Zanzibar are at risk<sup>79</sup>. Tanzania is the recipient Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) grants which have provided most of the funding for ACTs.

##### 4.1.1 Study area

The survey took place in 2 administrative Districts namely Kibaha and Kisarawe located in the East coast of the country. These were selected partly for convenience, similarity of malaria transmission patterns in the two districts, no major study like malaria vaccine testing had taken place in the two districts and that Kibaha and Kisarawe districts health facilities were among the 4800 health facilities in Tanzania which receive ACTs from MSD under the support of



GFATM funding. The districts are among the six administrative districts of the Coast region. The other districts are Mkuranga, Bagamoyo, Rufiji and Mafia (Map1 of Appendix 4). According to United Republic of Tanzania population census of 2002, the population of these districts is estimated at 226,560 persons with the age and sex distribution as shown in Table 1 of the Appendix 4.

Kisarawe district is bordered to the North by the Kibaha District, to the East by the Mkuranga District, to the South by the Rufiji District and to the West by the Morogoro Region. It covers an area of 3,555 km<sup>2</sup> along the coastal belt plains, with population of 95,614 people, it is made up of heterogenous ethnic groups mainly Zaramo, Ndengereko and Matumbi. There is one government owned district hospital, 3 health health centres in Maneromango, Masaki and Mzenga and 17 dispensaries, 12 of which are owned by the local government.

Administratively it is divided into 6 divisions, and 15 wards which are Kisarawe, Msimbu, Masaki, Kibuta, Marumbo, Maneromango, Msanga, Marui, Cholesamvula, Vikumbulu, Mafinzi, Kuruhi, Mzenga, Vihingo and Kiluvya. Kiluvya, Kisarawe, Msanga and Maneromango wards are mixed rural and urban settings while the rest are rural.

Kibaha district is located 40 km Northwest of Dar es Salaam. The district is bordered to the North by the Bagamoyo District, to the East by Dar-es-Salaam region, to the South by the Kisarawe District and to the West by the Morogoro Region. It covers an area of 1630 square kilometres. It is populated by 132,045 people. Administratively it is made up of 9 wards which are Tumbi, Kibaha, Magindu, Soga, Visiga, Ruvu, Mlandizi, Kwala, and Maili Moja. Kibaha, Tumbi, Mlandizi and Maili Moja wards are mixed urban and rural settings whereas the rest are rural. There is one designated district hospital at Tumbi, 2 health centres and 31 dispensaries (Figure 1).

The climate of both districts is tropical type characterized with high temperatures 28-32°C and high humidity. Although the climate supports growth of diverse cash crops such as coconut and cashewnuts; food crops such as cassava, maize and millet and fruits like pineapples and mangoes; it also favours survival and flourishing of main malaria vectors *Anopheles*

*gambiense* in rainy season and *Anopheles funestus* in the dry season. Malaria epidemiology in both districts is holoendemic, transmission being perennial with peaks during long rainy seasons (March to May) and during short rainy seasons (November to December).

Economically, the Coast region is among the 6 regions in the Mainland which are most deprived, majority of its people engaging in small scale farming and petty trading.

Kibaha and Kisarawe districts health facilities are among the 4800 health facilities in Tanzania which receive ACTs from MSD under the support of GFATM funding. For the most part, the roll out has gone smoothly and there have been no major supply issues to date. Beginning in July 2006, the NMCP began training on the new treatment guidelines for all health workers for example training of clinicians about ACTs, training of nursing and clinical staff on comprehensive case management including management and training in RDTs. Alu is currently available in the public health facilities. The most common antimalarial drug sold in the private sector drug outlets is SP and unsubsidized ACTs which are virtually unaffordable for the average rural Tanzanians

#### 4.1.2 Study population

The study population consisted of children aged less than 5 years brought by their caregivers to the primary health facilities in Kisarawe and Kibaha Districts, on a given day with fever and/or other symptoms suggestive of malaria. The age distribution of the population of the caregivers is shown in Table 3 of Appendix 4.

#### 4.1.3 Sample size

The sample size was calculated from 3 different proportions namely knowledge on malaria symptoms, malaria case management and diagnostic accuracy of clinical against laboratory malaria diagnosis using the formula,

$$N = \frac{1.5Z^2 p (1-p)}{\epsilon^2}$$

Where:

N = Minimum sample size

Z= Standard normal deviation corresponding to 95 % confidence level = 1.96.

p= Proportion under consideration

$\epsilon$  = Marginal error, which is 5% and variance inflation factor = 2.5

#### Sample size 1

Taking  $\epsilon$  =5%, Z= 1.96, p= 0.7 (70% of mothers could mention basic malaria symptoms in one study in Kenya<sup>101</sup>).

$N_1 = (322.7) (2.5) = 806$  for cluster sampling.

**Sample size 2**

Taking  $\epsilon = 5\%$ ,  $Z = 1.96$ ,  $p = 0.34$  (proportion of underfives appropriately managed for malaria in one survey in Tanzania = 34%<sup>26</sup>).

$N_2 = (344.8) (2.5) = 862$  for cluster sampling

**Sample size 3**

Taking  $\epsilon = 5\%$ ,  $Z = 1.96$ ,  $p = 0.69$  (proportion of children with clinically diagnosed malaria who had malaria parasites in the blood in a study in south-eastern Tanzania<sup>162</sup>).

$N_3 = (328.7) (2.5) = 823$  for cluster sampling

Sample size = 950 (taking the highest of the 3 sample sizes + 10% for possible non respondents)

**4.1.4 Sampling procedure**

Stage-wise cluster sampling technique was used. The eligibility criteria were that, the facility should be government owned (which receive ACTs from MSD under the support of GFATM funding) and a dispensary or a health centre without microscopy facility. The privately owned health facilities were not selected because most antimalarial drugs sold in the private health facilities are SP, artemisinin monotherapies and unsubsidized ACTs which are virtually unaffordable for the average rural Tanzanians. A sample of 20 health care facilities were randomly selected from 36 eligible health care facilities in the following manner; a sampling frame of all government health care facilities without microscopy facilities in Kisarawe and Kibaha Districts, was obtained from Coast region RMO office and each health care facility was assigned a number unique to itself. Each of the unique numbers was then written in a piece of paper (the pieces of paper looked similar). The papers were mixed up and another person apart from the investigator blindly picked up a paper bearing a number representing the particular facility. Mixing and picking up exercise went on until the required number of health care facilities was obtained. The numbers on the papers were disclosed at the end of sampling process. Due to practical problems as outlined in the study limitations, 17 health care facilities were visited.



#### **4.1.5 Inclusion and exclusion criteria**

##### **Inclusion criteria**

Any child aged less than 5 years presenting with fever or history of fever and/or other symptoms suggestive of malaria in absence of danger signs such as convulsions at the time of consultation, severe anaemia, prostration and coma.

##### **Exclusion criteria**

The children coming for follow up visits for chronic diseases (e.g. tuberculosis), traumas, burns, and patients referred or admitted for hospitalization were not recruited.

#### **4.2 Data collection**

##### **4.2.1 Tools and personnel**

Research tools that were used in this study included structured questionnaire to collect information from the care givers of the recruited children, information from the health care providers who were involved with recruited children and the health facilities in which the study was conducted. Blood specimens for examination of malaria parasites were collected from all the participating children using sterile blood lancets, absorbent cotton wool, methylated spirit and clean wrapped slides.

The data were collected by the principal investigator assisted by one to two assistants per each facility who were duly instructed on how to administer the interview and the filling in of the forms. One of the assistants assisted in taking the blood specimen for malaria parasite examination.

##### **4.2.2 Procedure in the field**

All the caregivers of sick children were interviewed when they had complete their health facility visit, to collect information on their sociodemographics, malaria symptom recognition in their children and actions taken within 24 hours of recognizing the symptoms, awareness of

policy change from the use of SP to Alu in the management of uncomplicated malaria and questions related to the use and dosages of Alu in the health facility and at home. Inquiries on important socioeconomic indicators (adapted from DHS) were used estimate the socioeconomic status of the caregivers. Prior to the interviews, informed consent was obtained from the caregivers. Interviewers determined the patient's age, weight, history of fever and other symptoms, axillary temperature, preliminary diagnosis, antimalarial drugs prescribed and counseling on the use of the prescribed drugs. Information was also collected from patient-held case notes to verify the information obtained from the caregivers. The health care providers involved in providing health care to the studied children were also interviewed to collect information on their demographics, pre-service and in-service training, working experience, access to national guidelines.

Finally, a health facility assessment was undertaken to record the availability of Alu and other antimalarials during the survey and in the past 6 months, the presence of functional weighing scales, thermometers, malaria treatment guidelines, and any displayed case-management wall charts.

#### **4.2.3 Laboratory procedure**

The blood slide for malaria parasites were taken from all presumptively diagnosed children and the specimens were then taken to Parasitology Laboratory at Muhimbili University of Health and Allied Sciences for further processing and examination. All the specimens were processed using Giemsa staining techniques under a regular method as elaborated in WHO Bench Aids for Malaria Diagnosis 2000 (Appendix 3).

World Health Organisation recommended method which compares the number of parasites in a thick blood film with the white blood cell count was adopted. The parasitaemia (parasite concentration) was estimated by counting the number of parasites per 200 white blood cells in a thick blood film.

### 4.3 Quality control

All the specimens were processed using the standard reagents eg Giemsa staining techniques using a regular method as described in WHO Bench to Aids Malaria Diagnosis 2000. The slides were then randomly reviewed by an independent, experienced laboratory technologist. Both examiners did not know the clinical presentations of the children whose slides were being examined. Furthermore the second laboratory technologist was not aware of the results reported by the previous colleague. In case of discrepancy the third opinion was taken.

### 4.4 Working definitions

**Caregiver** was a person involved in giving care to the studied child at the time of interview and from whom information about the child's illness and other information pertaining to the study were obtained. This could be the mother, the father or any other relative.

**Health care provider** was a person involved in providing the health care eg history taking, doing physical examination and prescribing and dispensing drugs to the studied child and providing counseling to the child's caregiver.

**Presumptive malaria diagnosis** is the diagnosis made by objective evaluation of symptoms presented by the caregiver and signs seen or detected by the health care provider.

**Laboratory confirmed diagnosis** is the diagnosis made based on the presence or absence of malaria parasites on the thick blood film preparation examined under light microscopy

**Parasite count** is the number of malaria parasites obtained by enumerating *Plasmodium* trophozoites in relation to the standard number of white blood cells (200 WBC in this study) on the thick blood film preparation examined under light microscopy.



### **Appropriate management of uncomplicated malaria in children aged less than 5 years**

The health care provider was said to have appropriately treated the child and hence adhered to national and IMCI guidelines if had asked for fever or history of fever and/or other symptoms suggestive of malaria such as loss of appetite, weakness, enlarged spleen, vomiting and diarrhea, examined for signs of anemia eg pallor and given appropriate antimalarial drug eg Alu in the right schedule and dosage<sup>64</sup> In settings where no microscopy is available, the following constitute criteria for diagnosing uncomplicated malaria and for prescribing Alu in children aged less than 5 years<sup>64</sup>,

1. Any child aged less than 5 years,
2. Weighing more than 5 kilograms,
3. Presenting with fever or history of fever and/or other symptoms suggestive of malaria such as loss of appetite, weakness, enlarged spleen and vomiting/diarrhea,
4. Pallor,
5. In absence of danger signs eg prostration, coma, respiratory distress, convulsions, vomiting everything,
6. No prior or correct use of ACTs,
7. First line of antimalarial drug recommended for uncomplicated malaria in a right time schedule and dosage,
8. Appropriate counseling,

In settings where no microscopy is available the children presenting with fever or history of fever, were examined for pallor and prescribed with first line of antimalarial drug recommended for uncomplicated malaria in a right time schedule and dosage were given score of 1 and any other criteria which does not define appropriate malaria case management in IMCI and malaria treatment guidelines were given score of 0. Appropriate management was declared when the score was above 2.



**Knowledge of the symptoms of uncomplicated malaria in children**

Caregivers were asked how they recognize uncomplicated malaria in a child aged less than 5 years and were allowed to give spontaneous responses which were recorded and scored as follows:

1. Fever
2. Body weakness
3. Vomiting and diarrhea
4. Poor appetite
5. Pallor
6. Headache
7. Joint pains
8. Body ache
9. Cough
10. Painful urination
11. Weight loss

The symptoms numbered 1-5 are commonest in underfives and here they each carried a score of 2, symptoms numbered 6-9 are less common in underfives and here they each carried a score of 1 and while those numbered 10-11 do not apply in acute malaria infections, hence each carried a score of 0.

Total score

12 or above = Good knowledge

5 - 11 = Moderate knowledge

0 - 4 = Inadequate knowledge

Moderate and good knowledge categories were then combined in the examination of factors influencing knowledge as a single category namely adequate knowledge.

### **Knowledge of Alu dosages and time schedules**

The correct responses to the question pertaining to the following statements about use of Alu were recorded and each carried a score of 1

1. The first dose taken at the health facility
2. Alu dosages taken with foods/drinks
3. Recommended meals to be taken with Alu, fatty meals and milk
4. The second dose taken after 8 hrs
5. Children with malaria take 6 doses of Alu
6. In case of vomiting dose was to be repeated within half an hour
7. In case of vomiting and the dose is repeated, the caregiver asks for replacement dose at health care facility
8. Caregiver expects resolution of symptoms after two days
9. Caregiver goes on to finish the dose even if the symptoms resolve within the expected time period
10. Caregiver goes back to the health facility if the symptoms do not resolve within the expected time period.

Total Score

8-10 Good knowledge

5-7 Moderate knowledge

0- 4 Inadequate knowledge

Moderate and good knowledge categories were then combined in the examination of factors influencing knowledge as a single category namely adequate knowledge.

Quality of counseling given to the caregivers regarding Alu use included asking whether the following was done by the health care providers; the explanation on how to take Alu at home, administration of the first dose at health facility, advice to take Alu after the meal, to complete all doses, what to do in case of vomiting and follow up. Each carried a score of one (Appendices 1 and 2)

#### 4.5 Study variables

**Table 1 Study variables**

Factors to be examined	Dependent variable	Independent variables
Factors influencing Alu prescription in underfive children	Antimalarial prescribed  Alu prescribed	Child's age, weight, main complaints, symptom duration, consultation time, antimalarials availability, health care provider's professional training, experience and his/her attendance to in-service training.
Factors influencing appropriateness of malaria case management	Quality of care	Child's age, weight, main complaints, symptom duration, consultation time availability of antimalarials, presence of treatment guidelines, health care provider's professional training and experience.
Factors influencing knowledge on the correct use of artemether-lumefantrine under directly observed therapy and subsequent administration at home.	Knowledge on correct use of ALU	Age and sex of the caregiver, the caregiver's education level, socioeconomic status, religious affiliation.
Factors influencing knowledge on malaria symptoms by the caregivers.	Knowledge on malaria symptoms	Age and sex of the caregiver, the caregiver's education level, socioeconomic status, religious affiliation
Factors influencing care seeking within 24 hours of symptom onset	Symptom duration	Age and sex caregiver, the care giver's education level, socioeconomic status and religious affiliation
Factors influencing the quality of Alu counseling	Quality of counseling	health care provider's professional training and experience and the his/her attendance to in service training.

#### 4.6 Pre-testing of research tools

Pre-testing of research tools was done in the primary health facility in Kibaha after obtaining ethical clearance. This was then followed by appropriate changes in the questionnaire before



its final use in the target population; by making sure that the questions were clearly worded, specific, and appropriate for the population and followed in a logical fashion.

#### **4.7 Data management and statistical analysis**

##### **4.7.1 Data preparation, entry, cleaning and validation**

The incoming questionnaire data were revisited to see that responses were complete and readable, all important questions were answered and all the relevant information was included.

The template for data capturing was prepared in the Microsoft Excel 2003 where incoming questionnaires were entered. The data were then spot checked on random basis for accuracy by referring to the original questionnaires. The entered data were summarized to check that all the data are within acceptable limits and boundaries.

##### **4.7.2 Descriptive statistics**

The analyses were performed using EPI Info Computer software version 3.5.1 Aug 2008, Public Health Domain Software, CDC, Atlanta, Georgia, USA. Descriptive analysis was done at the health facility, health worker, the patient and the caregiver level. A stepwise approach was applied in analyzing quality of malaria case-management for patients who needed to have antimalarials prescribed according to guidelines. First, treatment practices were analyzed for all subjects who were eligible to receive antimalarials, that is, those who had presumptive diagnosis of malaria, and then, analysis was restricted to subjects who were given Alu in facilities where Alu was in stock during the time of the survey. Finally, the quality of Alu counseling practices was restricted to children who were prescribed Alu and counseled at the facility. Descriptive data were presented as frequencies and proportions, with corresponding 95% confidence intervals (CIs). Proportions of patients with laboratory confirmed malaria were compared with proportions with presumptively diagnosed malaria using analytical cross-tabulations.



### 4.7.3 Inferential statistics

The relationship between studied variables and the determinant factors (Table 1 above) were examined using analytical cross-tabulations in which odds ratio (OR) and 95% confidence interval (2x2 cross-tabulations) and  $\chi^2$  and *P*-values (2xk cross-tabulations) were estimated for each factor. This was then followed with application of multiple logistic regression for factors with significance level <0.05. Hypothesis testing and confidence interval estimations were done at an alpha level of 0.05.

### 4.8 Study limitations and sources of error

#### Practical problems

1. Few malaria cases due to seasonal variations making recruitment slower than expected because of low malaria transmission in the study areas in the period from June to January.
2. Ineffective public transport system, hence need for hiring motorcycles which was expensive and risky.
3. Inoperative facilities  
One of the selected facilities was not operating because the building was damaged by rain, in another facility the construction was not yet finished and another one which could not be reached by motorcycle (Gwata dispensary in Kisarawe could be reached by railway transport).
4. Auto fixation of the slides. This is the process through which blood films gradually become fixed through exposure to the atmosphere and high temperature. This happened because health care facilities without microscopy facilities had no appropriate rooms where slides could be kept from dust prior to further processing.

**Sources of errors**

1. Hawthorne effect is a form of confounding which occurs when research study participants know that they are being studied and alter their performance because of the attention they receive from the experimenters.

**4.9 Ethical issues**

Ethical clearance was obtained from Muhimbili University of Health and Allied Sciences Research Ethical Committee. Permission to conduct research was obtained from relevant authorities including MOHSW, Coast region RMO, District Executive Directors, District Medical Officers and the Clinical Officers In-charge of the health facilities. Each study participant was informed on aims and procedures of the study. Consent was obtained from each caregiver of the selected child.

## CHAPTER 5

### 5.0 RESULTS

#### 5.1 Enrolment

The study enrolled, 934 underfive children who were brought to the health care facilities by their caregivers with complaints of fever and / or other symptoms suggestive of malaria. Of the 934 caregivers of the enrolled children, 916 completed the interview and blood specimens for malaria parasite examination was taken from their children. There were 18 caregivers who could not complete the interview so were excluded from the subsequent procedures. Some of these missed subjects could not wait and others had their children crying so calm and conducive environment for the interview could not be established. Participation rate was 98.1%. Of the health care providers who were involved in providing the health care such as history taking, doing physical examination and prescribing and dispensing drugs to the children and providing counseling to the caregivers, 12 out of 17 were interviewed, 3 could not be available for interview and 1 refused to participate. Each of the health care providers 12 interviewed, was involved in providing the health care at least one enrolled child.

#### 5.2 Health care providers and health care facility characteristics

Of the health care providers interviewed, 6 were Clinical Officers and 6 were nurses (nurse midwives and assistant nurses). All the health care providers interviewed had attended in-service training workshops on the use of Alu in the management of uncomplicated malaria. Among these, 6 had a working experience of more than 5 years, 2 had less than 2 years of working experience, 6 perform more than 40 consultations per day (includes all patient categories) and 4 perform less than 20 consultations per day.

Malaria treatment guidelines were available in 7 facilities 7 had 3-4 health workers while 5 had more than 4 health care providers. Three facilities served less than 30 outpatients per day while 9 facilities served more than 30 outpatients per day (overall average of 44 patients per day). Four facilities had Alu alone in stock as an antimalarial during the time of interview



whereas the remaining 8 had in stock amodiaquine, SP, quinine, Alu and other artemisinin monotherapies like rectal and parenteral artesunate.

### **5.3 Characteristics of the studied children and their caregivers**

#### **5.3.1 Demographics and socioeconomic status**

Of the 916 studied children, 240 (26.2%) were infants (0-1 years) and 439 (47.9%) were above 2 years of age, 763 (83.3%) weighed between 3 to 15 kilograms while 9 (1%) weighed above 25 kilograms. Male to female ratio was 49.7% to 50.3%.

The age range for the 916 caregivers interviewed was between 10 to 64 years with median age of 29 years. The modal age group was 20-29 years in the sample as well as in the general population. Of the interviewed caregivers, there were 171 caregivers (18.7%) who had informal education, 669 (73%) had primary education and 22 (2.4%) had secondary education (Table 2a and Table 2b).

The main religious groups represented in the study were Muslims 664 (72.5%). Christians were 166 (18.1%) while traditionalists and other religious groups together represented 9.4%. Majority of the caregivers, that is 689 (75.2%) were in the middle socioeconomic status while 23.3% were in the low socioeconomic status. Only minority (1.5%) were in the higher economic status. Those who had 1-3 children to take care of were 626 (67.7%) while those who had 3-6 children to take care of were 250 (27%). The remaining 4.3% had more than 6 children to take care of. Married caregivers were the majority (47.1%), followed by those in cohabiting relationships (26.3%). The singles made up 16.1% of the caregivers (Table 2b).



**Table 2a Baseline characteristics of 916 studied children**

Study population	Number (%)
Child's age (months)	
3 - 11	240 (26.2)
12 - 23	237 (25.9)
24+	439 (47.9)
Child's weight (kgs)	
5-15	763 (83.3)
15-25	94 (10.3)
25 and above	9 (1.0)
Child's sex	
Male	451 (49.7)
Female	456 (50.3)

**Table 2b Baseline characteristics of the caregivers**

Age of the caregiver (years)	Number (%)
10-19	51 (5.6)
20 - 29	506 (55.2)
30 - 39	262 (28.6)
40 +	97 (10.6)
Education level of the caregiver	
Informal	171 (18.7)
Primary	669 (73.0)
Secondary and above	23 (2.5)
Religious affiliation of the caregiver	
Traditionalists	9 (1.0)
Muslims	664 (72.5)
Christians	166 (18.1)
Marital status	
Single	147 (16.1)
Married	431 (47.1)
Cohabiting	241 (26.3)
Socioeconomic status	
Low	213 (23.3)
Middle	689 (75.2)
High	14 (1.5)

### 5.3.2 Care seeking, consultation attributes and illnesses

Of the 916 caregivers 469 (51.2%) sought health care for their children within 24 hours of the onset of the symptoms (Table 3a) and 570 (62.2%) spent more than 5 minutes in the consultation. The five (5) topmost main presenting symptoms were fever 834 (91.0%), cough (2.1%), diarrhoea (2.0%), poor appetite (1.0%) and headache (0.9%). Of the children who had fever as main complaint, 464 (55.6%) were found to have axillary temperature above 37.5°C. Of those who had no fever as main complaint (81) had their axillary temperature taken and (57), 25(43.9%) of them were found to have axillary temperature above 37.5°C. Malaria illness as was defined by history of fever and other symptoms was suspected in 846 patients (92.4%). Few that is 70, (7.6%) had diagnoses other than malaria. RDT was done on 112 of the children suspected to have malaria and it was reactive in 65 (58.0%) of them. Other clinical diagnoses that were made included RTI, UTI, GII and skin infections.

### 5.3.3 Prescribed drugs and counseling

Of the 846 children who were presumptively diagnosed as having malaria, 713 (84.3%) were prescribed Alu, 67 (7.9%) were prescribed rectal or parenteral artemisinin monotherapies or amodiaquine, 49 (5.8%) were prescribed quinine and 17 (2.0%) were prescribed SP. Of those who had no malaria as presumptive diagnosis, 10 (14.3%) were given Alu and 2 were given quinine (Table 3b).

Altogether, a total of 723 children were prescribed Alu (Table 3b). Among these 608 (84.1%) took their first dose at the health facility and 716 (99%) were counseled on how to use the drugs. However, only 459 (85.4%) were sufficiently counseled (Table 3b).

## 5.4. Caregivers' knowledge

### 5.4.1 Knowledge of the caregivers on malaria symptoms

Of the 916 caregivers examined on the knowledge and recognition of malaria symptoms in children under five years of age, 324 (35.4%) could mention correctly at most 2 commonest symptoms or less than 4 less common symptoms of uncomplicated malaria in children aged less than 5 years, 387 (42.2%) mentioned 3 to 4 symptoms and 205 (22.4%) had good knowledge as it is shown in Table 3a.

### 5.4.2 Caregivers' knowledge on the correct use of artemether-lumefantrine

Eight hundred and forty eight out of 916 caregivers (85.4%) were aware of the treatment policy change from SP to Alu, most of them having heard from radio and seen in television broadcasts and through health education given in the health facilities, 534 (58.3%) had good knowledge, 272 (29.7%) had moderate knowledge and 110 (12.0%) had poor knowledge as shown in Table 3a.

**Table 3a Knowledge of the caregivers and care seeking**

Variable	Number	(%)
Knowledge on symptoms of uncomplicated malaria		
Low	324	(35.4)
Moderate	387	(42.2)
Good	205	(22.4)
Knowledge on Alu dosage and use		
Low	110	(12.0)
Moderate	272	(29.7)
Good	534	(58.3)
Care seeking		
Within 24 hours	469	(52.9)
Beyond 24 hours	418	(47.1)



**Table 3b Illness attributes and care of the children**

Variable	Number	(%)
Main presumptive diagnosis		
Malaria	846	(92.4)
Not malaria	70	(7.6)
Main drugs prescribed		
+SP	17	(2.0)
+Quinine	51	(5.8)
+ Alu	723	(84.3)
+AM <sup>1</sup>	67	(7.9)
-SP	0	(0.0)
-Quinine	2	(2.9)
-Alu	10	(14.3)
Case management		
Inappropriate	386	(42.1)
Appropriate	530	(57.9)
Counseling on Alu use		
Not sufficient	264	(36.5)
Sufficient	459	(63.5)

**Key**

+AM<sup>1</sup>= artemisinin derived monotherapies eg rectal and parenteral artesunate and amodiaquine prescribed to those who had presumptive malaria diagnosis,

+ = antimalarials prescribed to those who had presumptive malaria diagnosis

- = antimalarials prescribed to those who had no presumptive malaria diagnosis

**5.4.3 Factors affecting caregivers' knowledge on malaria symptoms and Alu use**

The factors affecting caregivers' knowledge on malaria symptoms and correct use of artemether-lumefantrine under directly observed therapy and subsequent administration at

home were examined and they are outlined in the variables (Table 1 page 38). Caregivers with moderate to high socioeconomic status were more likely to have moderate to good knowledge of symptoms of uncomplicated malaria in children aged less than 5 years (70.4%) than caregivers with low socioeconomic status (P value < 0.0001), (Table 4).

**Table 4 Factors affecting care giver's knowledge on malaria symptoms**

Factor	Category	Number (% with moderate to good knowledge)	$\chi^2$	P value
Age group in years	10-19	29 (56.9)	1.6	0.4
	20-39	498 (64.8)		
	40-69	63 (67.7)		
Sex	Male	85 (63.0)	1.2	0.3
	female	495 (67.7)		
Level of education	Informal	110 (64.3)	1.6	0.4
	Primary	461 (68.9)		
	Secondary and above	16 (73.9)		
Socio economic status	Low	97 (45.5)	44	<0.0001
	Moderate to high	495 (70.4)		
Religious affiliation	Traditional	5 (55.6)	1.9	0.37
	Christianity	122 (73.5)		
	Islam	461 (69.4)		

Furthermore, socioeconomic status (P value < 0.0001) was found to be associated with caregivers' knowledge on correct use of Alu under directly observed therapy and subsequent use at home (Table 5)

**Table 5 Factors affecting knowledge on Alu use**

Factor	Category	Number (% with moderate to good knowledge)	$\chi^2$	P value
Age	10-19 years	43 (84.3)	1.8	0.4
	20-39 years	674 (87.8)		
	40-69 years	89 (92.0)		
Socioeconomic status	Low	134 (62.9)	165	< 0.0001
	Mod to high	672 (95.6)		
Sex	Male	124 (91.9)	0.08	0.8
	Female	666 (91.1)		
Religious affiliation	Traditional	8 (88.9)	5.6	0.06
	Chritianity	154 (92.8)		
	Islam	641 (96.5)		
Education level	Informal	159 (93.0)	0.17	0.9
	Primary	617 (92.2)		
	Secondary and above	20 (90.9)		

#### 5.4.4 Factors affecting early care seeking by caregivers

Of the factors examined, caregivers with moderate to good knowledge on malaria symptoms (P value <0.001) and caregivers who were married (P value = 0.004), were found to more likely seek care early (within 24 hours of the onset of the malaria symptoms in their children). Multiple logistic regression analysis on these factors, showed that moderate to good knowledge of symptoms of uncomplicated malaria among caregivers of underfives were strongly associated with care seeking within 24 hours of onset of symptoms (OR= 1.5,95%CI:1.3-1.9)



**Table 6 Factors affecting early care seeking by the care givers**

Factor	Category	Number (% who sought care within 24 hrs)	$\chi^2$	P value	Adjusted OR(95%CI)
Age group in years	10-19	22 (45.8)	2.2	= 0.3	
	20-39	393 (52.6)			
	40-69	54 (58.7)			
Sex	Male	62 (46.3)	3.5	= 0.06	
	Female	390 (55.0)			
Level of education	Informal	79 (47.0)	3.5	= 0.17	
	Primary	357 (54.8)			
	Secondary	13 (59.1)			
Socio economic status	Low	93 (48.9)	1.6	= 0.45	
	Middle to high	376 (53.9)			
Religious affiliation	Traditional	3 (33.3)	2.1	= 0.3	
	Christian	92 (55.4)			
	Islam	341 (51.4)			
Knowledge on symptoms of malaria	Inadequate knowledge	137 (45.5)	9.9	<0.001	1.5 (1.3-1.9)
	Adequate knowledge	332 (56.7)			
Marital status	Single	66 (45.2)	11	= 0.004	1.07 (0.9-1.3)
	Married	247 (57.4)			
	Cohabiting	109 (46.2)			

### 5.5. Quality of case management and prescription of antimalarials

Of the 916 children brought to the health care facilities with fever or history of fever and/or other symptoms suggestive of malaria, 530 (57.9%; 95%CI (54.6-61.1) patients were appropriately managed according IMCI/ malaria treatment guidelines. Of the children on whom malaria was suspected (n=846), 527 (62.3%; 95%CI (58.9-65.6) were appropriately managed according IMCI/ malaria treatment guidelines.

Appropriate malaria case management was more likely to be provided to children on whom malaria was suspected and had history of fever (N=793, 523(66%), 95%CI: 62.5-69.2). It was

also likely in children in whom axillary temperature was above  $37.5^{\circ}\text{C}$  ( $N=475$ ,  $333(70.1\%)$ ,  $95\% \text{ CI: } 65.7-74.1$ ), (Table 7).

In an analysis of treatment quality from the patient's perspective, that is, the patient took the first dose at the facility and the caretaker was sufficiently counseled on the importance of finishing the prescribed dose, when to return immediately as in case of vomiting or worsening of symptoms, importance of food and fluid intake and to return for follow up;  $608$  ( $84.1\%$ ,  $95\% \text{ CI: } 81.6-86.6$ ) took the first dose of Alu at the health care facility. Counseling was given to  $716$  ( $99\%$ ,  $97.9-99.0$ ) of the caregivers whose children were prescribed Alu. However, it was sufficiently done in  $459$ ,  $95\% \text{ CI: } 59.8-67.0$ ) of the caregivers whose children were prescribed Alu. The quality of counseling was strongly associated with the counseling by the clinical officer ( $\text{OR}=2.46$ ,  $95\% \text{ CI: } 1.9-3.2$ ) and also by the counseling by the health care provider with working experience of more than 2 years ( $\text{OR}= 2.2$ ,  $95\% \text{ CI: } 1.6-2.9$ ).

**Table 7 Quality of malaria case management by malaria diagnosis category**

Malaria diagnosis category	Number (% appropriately managed)
Overall	530 (57.9%)
Presumptive malaria	527 (62.3%)
Presumptive malaria+ h/o fever	523 (66%)
Presumptive malaria no h/o fever	4 (7.5%)
Presumptive malaria temperature > 37.5°C	333 (70.1%)
Presumptive malaria Temperature <37.5°C	81 (56.3%)
No Presumptive malaria	3 (4.3%)
No presumptive malaria +h/o fever	3 (7.1%)
No presumptive malaria no h/o fever	0 (0%)
No presumptive malaria Temperature > 37.5°C	3 (21.4%)
No presumptive malaria Temperature <37.5°C	0 (0%)

### 5.5.1 Factors affecting the quality of case management and prescription of Alu

Of the factors examined (Table 1 page 38), the following were found to strongly influence the quality of management given to the sick underfive child suspected to have malaria ; a child with fever as main presenting symptom (OR=23.8,95%CI:8.5-66.6), care sought within 24 hours of onset of symptoms (OR=1.5, 95%CI:1.2-2.0), consultation time more than 5 minutes (OR=1.8,95%CI:1.3-2.3), Alu alone available (OR=2.2, 95%CI:1.5-3.2), consultation by a clinical officer (OR=1.5, 95%CI:1.09-1.9), and consultation by health care provider with experience of more than 2 years (OR=1.45,95%CI:1.04-2.0), (Table 8). Multiple logistic regression analysis on these factors showed that presence of fever or history of fever as main



presenting symptoms (OR = 25, 95%CI:(7.8-84), consultation time more than 5 minutes (OR=2.3 (1.5-3.5) and presence of Alu alone as an antimalarial OR= 1.4 (1.1-1.7) were significantly associated with the appropriate quality of case management given to the children with suspected malaria.

**Table 8 Factors affecting appropriate malaria case management among those who had presumptive malaria diagnosis**

Factor	Category	% appropriately managed	Crude OR(95%CI)	P value	Adjusted OR(95%CI)
Main presenting symptom	Fever	66.0	23.8 (8.5-66.6)	< 0.0001	25 (7.8-84)
	No fever	7.5			
Duration of symptoms	Within 24 hours	67.7	1.4 (2-1.1)	= 0.006	1.2 (0.8-1.7)
	Above 24 hours	58.5			
Consultation time	Less than 5 minutes	50.2	1.8(1.3-2.3)	= 0.0002	2.3 (1.5-3.5)
	More than 5 minutes	63.9			
Presence of treatment guidelines	Present	56.1	0.9 (1.2-0.6)	= 0.3	
	Not present	59.6			
Antimalarials available	Alu alone	71.3	2.2 (3.2-1.5)	< 0.0001	1.4 (1.1-1.7)
	Alu with *others	52.7			
Healthcare provider's professional training	Clinical officer	65.2	1.5 (1.9- 1.09)	= 0.01	1.1 (1-1.3)
	Not clinical officer	56.3			
Healthcare provider's working experience (years)	0-2 years	52.4	1.5,(1.04-2.0)	= 0.013	1.1 (0.9-1.3)
	2 and above	61.4			

\*others = SP, quinine, amodiaquine, artemisinin derived monotherapies

### Prescription of Alu

The following factors were found to have significant influence on prescription in children suspected to have uncomplicated malaria; age above 1 year (OR=1.5 (1.1-2.1), fever as main presenting symptom (OR=3.6,95%CI:2.2-5.7), consultation time more than 5 minutes (OR=2.1, 95%CI:1.5-2.9), Alu alone available as an antimalarial (OR=2.6, 95%CI:1.6-4.1), consultation by a clinical officer (OR=2.6, 95%CI:1.6-5.0) and care seeking within 24 hours of onset of symptoms ( OR=1.7,95%CI:1.2-2.3).

Multiple logistic regression analysis on these factors showed that, prescription of Alu in correct doses and time schedules was strongly associated with consultation by a clinical officer (OR=1.2, 95%CI: 1.1-1.4), consultation time of more than 5 minutes (OR=1.9, 95%CI: 1.2-2.9), and where Alu alone was available as an antimalarial (OR= 1.4, 955CI:1.1-1.8).

**Table 9 Factors affecting prescription of Alu**

Factor	Category	%	Crude OR (95%CI)	P value	Adjusted OR(95%CI)
Children age group in months	2-11	73.8	1.5 (1.1-2.1)	= 0.02	1.1 (0.9-1.4)
	12+	80.8			
Main presenting symptom	Fever	81.3	3.6 (2.2-5.7)	< 0.0001	1.8 (0.9-3.3)
	No fever	54.9			
Duration of symptoms	Within 24 hrs	83.6	1.7 (1.2-2.3)	= 0.002	1.3 (0.9-1.9)
	Above 24 hrs	75.4			
Consultation time	Less than 5 min	71.4	2.1 (1.5-2.9)	< 0.0001	1.9 (1.2-2.9)
	More than 5 min	83.9			
Available antimalarials	Alu alone	87.3	2.6 (1.6-4.1)	< 0.0001	1.4 (1.1-1.8)
	Alu and *others	72.9			
Health care provider's professional training	Clinical officer	96.1	2.6 (1.6-5)	< 0.001	1.2 (1.1-1.4)
	Non clinical officer	90.1			

\*others = SP, quinine, amodiaquine, artemisinin derived monotherapies

## 5.6 Comparison of clinical malaria diagnosis and laboratory confirmed diagnosis.

### 5.6.1 Proportion of children with clinically diagnosed malaria that have laboratory confirmed malaria diagnosis.

Malaria parasites were found in 186 of 750 blood smears examined. Overall infection rate (slide positivity rate), was 24.8%, (95%CI: 21.8-28.1). Proportion of children with clinically diagnosed malaria who had laboratory confirmed malaria diagnosis was 26.0 % (95%CI: 22.8-29.5) (Table 10).

**Table 10 Laboratory confirmed malaria diagnosis by age and clinical presentation (n=750)**

Clinical presentation category	Number (% with parasitemia)	
Overall	186	(24.8)
Presumptuous malaria	179	(26.0)
Fever as main symptom	177	(26.0)
Symptoms other than fever	9	(12.9)
Main diagnosis other than malaria	7	(11.5)
Children age group (months)		
2-11	39	(18.7)
12-23	52	(27.1)
24+	95	(27.2)

The proportion of patients with trophozoites more than 1000 per 200 white blood cells were 8% (60/750, 95%CI: 6.2-10.2). Infection rate as well as parasite density greater than 1000 trophozoites per 200 white blood cells was low in the infants (age 2-11 months), (Table 10) and the density increases as the age increases (Table 11).

**Table 11 Parasite count by age (n=750)**

Age in months	Number (% with parasite count >1000/200 WBC)	
2-11	9	(4.3)
12-23	18	(9.4)
24+	33	(9.5)
Total	60	(8.0)



The proportion of children who tested positive for malaria and were prescribed Alu was 83.9% (95%CI: 77.9-88.5) and there were 5 children with laboratory confirmed malaria who were not prescribed any antimalarials. The proportion of children who tested negative for malaria and were prescribed Alu was 86.0 % (95%CI: 82.8-88.8), (Table 12)

**Table 12 Children with laboratory confirmed malaria who were given antimalarials**

Prescribed antimalarials	Children with laboratory confirmed malaria who were given antimalarials			
	Positive		Negative	
Laboratory confirmed malaria	Number	(%)	Number	(%)
SP	2	(1.1)	11	(2.1)
Quinine	13	(7.0)	30	(5.8)
Alu	156	(83.9)	444	(86.0)
AM <sup>1</sup>	10	(5.2)	31	(6.0)
*	5	(2.3)		

AM<sup>1</sup> = artemether derived monotherapies or amodiaquine

\* = children with laboratory confirmed malaria who were not prescribed any antimalarials

### 5.6.2 Diagnostic accuracy of clinical malaria diagnosis against laboratory confirmed diagnosis

The results in Table 13 show that positive predictive value (PPV), that is, post-test probability of disease in clinically diagnosed malaria = 0.26 and negative predictive value (NPV), that is, post-test probability of absence of disease in children clinically diagnosed not to have malaria = 0.885.

Post-test probability of absence of disease in clinically diagnosed malaria is (1-PPV) = 0.74 that is positive clinical diagnosis criteria have high chance of ruling in large numbers of false

positives. Post-test probability of presence of disease in children clinically diagnosed not to have malaria is  $(1\text{-NPV}) = 0.115$ , that is, negative clinical diagnosis rules out few cases, who have the disease. False positive rate  $(\alpha) = \text{FP} / (\text{FP} + \text{TN}) = 510/564 = 0.904$ . False negative rate  $(\beta) = \text{FN} / (\text{TP} + \text{FN}) = 7/186 = 0.038$ . Power of the test (clinical malaria diagnosis) is  $1 - \beta = 0.962$ .

Likelihood-ratio positive = power/false positive rate = 1.06 (95%CI; 1.02-1.1), Likelihood-ratio negative = false negative rate/1-false positive rate =  $0.038/0.096 = 0.4$  (95%CI: 0.18-0.85). With  $\text{LR}+ > 1$  and  $\text{LR}- < 1$  and, clinical malaria diagnosis is associated with the presence of the disease and negative clinical malaria diagnosis is associated with the absence of disease respectively (OR= 2.7, (95%CI: 1.2-6.1).

Furthermore with large numbers of false positives and few false negatives, a positive clinical malaria diagnosis is in itself poor at confirming a true case of malaria (PPV = 26%) and so further investigations eg RDTs and microscopy must be undertaken.

**Table 13 Comparison of clinical and laboratory diagnosis of malaria**

Clinical diagnosis	Laboratory confirmed diagnosis			LR (95%CI)	OR(95%CI)	P value
	Negative	Positive	Total			
Positive PPV (%)	510	179 26.0	689	1.06(1.02-1.1)	2.7(1.2-6.1)	0.01
Negative NPV (%)	54 88.5	7	61	0.39 (0.18-0.85)		

## CHAPTER 6

### 6.0 DISCUSSION

The goal of appropriate malaria diagnosis and treatment is to reduce morbidity, mortality and economic losses and to encourage rational drug use in order to minimize the development of drug resistance. The use of malaria diagnosis and treatment guidelines is the tool to achieving this goal.

One major observation in the findings of this study is that, overall performance in the childhood malaria case management practices, three years after adoption of Alu as first line treatment of uncomplicated malaria in Tanzania Mainland has not reached the RBM/WHO<sup>6</sup> set target of appropriately managing 80% malaria in children by 2010.

However, 51.2% of caregivers sought care within 24 hours of the onset of the symptoms, 64.6% could mention correctly at least 2 commonest symptoms or more than 4 uncommon symptoms of uncomplicated malaria in children aged less than 5 years, 62.3% of patients who had suspected malaria were correctly managed according to IMCI/treatment guidelines, 63.5% were sufficiently counseled, and 58.3% had good knowledge on correct use of artemether-lumefantrine. The three (3) years period could have provided an ample time for healthcare providers to familiarize with the new guidelines and translate the new policy into appropriate clinical practice. Moreover, artemether-lumefantrine was available in all the health facilities visited and all the health care providers interviewed had attended the in service training on the use of artemether-lumefantrine for management of uncomplicated malaria. However, the Hawthorne effect could have resulted in better performance as seen in the prescription of antimalarials in all suspected cases of malaria, among which 84.3% were artemether-lumefantrine.

The fact that retrospective data for artemether-lumefantrine prescribed in the last 6 months prior to the survey was not significantly different from the quantity prescribed during the time of survey (2160 packs prescribed during the survey period against 2290 used in the preceding



6 months), the Hawthorne effect alone cannot be as an explanation for this performance. This is in agreement with studies done in Uganda<sup>80</sup>, Zambia<sup>25</sup> and Angola<sup>81</sup>. The findings though encouraging, they show us that we are still lagging behind the target.

### **6.1 Factors affecting the quality of care, prescription of Alu and other antimalarials**

The quality of management given to the child suspected to have malaria was found to be strongly associated with presumptive malaria diagnosis. As it was seen in another study there is a tendency for healthcare providers to manage appropriately the disease they suspect<sup>81</sup>. The appropriate malaria case management in underfives was also strongly associated with presence of fever or history of fever as main presenting symptom; care sought within 24 hours of onset of symptoms; consultation time of more than 5 minutes, the presence of Alu alone in the health care facility; consultation was by a clinical officer consultation was by health care provider with experience of more than 2 years. Only 7.1% of children in whom no malaria was suspected and had history of fever were managed appropriately for malaria. Similar studies in Uganda<sup>80</sup> show similar results in that 16% of febrile patients were not treated at all with any antimalarials and that healthcare workers were likely to treat according to guidelines if fever were reported spontaneously.

Objective assessment of fever and other symptoms by careful examination and measurement has been shown to improve case management quality<sup>81</sup> even if the caregiver does not mention fever as a main complaint. Solely relying on main complaint alone could lead to a lot of missed cases of febrile illness who will not be appropriately managed. This is also reflected from the improved quality of care and increased tendency to prescribe Alu as the consultation time period increases.

Presence of other antimalarials along with Alu negatively affects prescription of Alu to the patients who need it. The negative influence of non recommended antimalarials on prescription of Alu has also been noted in other studies in Uganda<sup>80</sup> and in Kenya<sup>82</sup>. The reasons as to why non recommended drugs were prescribed even in the presence of effective and recommended drug given in other studies<sup>82</sup> were fear by the healthcare provider of

possibility that Alu would run out of stock, excessive stocks of non recommended antimalarials, perceived severity of the illness and caregiver's choice.

Consultations attended by clinical officers and consultations which took more than 5 minutes were positively associated with Alu prescribed in correct doses and time schedules. This association was also featured in the quality of counselling given to the caregivers.

In this study, positive association of drug prescription with professional training and working experience of the healthcare provider contrasts with other studies in Benin<sup>83</sup> and Uganda<sup>80</sup> and systematic review elsewhere<sup>84</sup>, where clinicians and more experienced healthcare providers seemed to disrespect treatment guidelines compared to other cadres like nurses. This might be attributed to incorporation of IMCI in the pre-training of clinical officers and in-service training on the management of uncomplicated malaria using Alu. The implication is that appropriate training in both pre-service and in-service might facilitate healthcare providers to adhere to new treatment policy and foster its swift adoption in rural settings where reliable diagnostic facilities are lacking.

## **6.2 Factors affecting early care seeking**

Although 64.6% of caregivers correctly knew at least 2 commonest symptoms or more than 4 uncommon symptoms of uncomplicated malaria in underfives, proportion of children who accessed modern healthcare for malaria within 24 hours of onset of symptoms was only 51.2%. However, the caregivers' knowledge on uncomplicated malaria symptoms was found to be strongly associated with the care-seeking within 24 hours of the onset of the malaria symptoms.

This finding agrees with studies done in Malawi<sup>85</sup> and in Uganda<sup>86</sup> in which, despite high knowledge of malaria, prompt treatment and health-seeking behaviour were poor, with the majority of children first being managed at home with treatment regimens other than effective antimalarials. Elsewhere, it was also found that more than half of caregivers used the official health sector or village health workers at some point, with delays averaging three or more



days<sup>87</sup>. The quality of case management being positively associated with early care seeking within 24 hours of symptom onset, there is a need that sociocultural and behavioural factors in the community<sup>39</sup> as well as healthcare system<sup>80,82</sup> be found out and addressed in qualitative research so that knowledge and practices pertaining to effective management of malaria will produce the expected outcomes.

### **6.3 Knowledge of malaria symptoms and correct use of Alu in underfive year children among the caregivers**

The moderate to high socioeconomic status was found to have strong association with knowledge of uncomplicated malaria symptoms in children under five years of age. It was also found to be significantly associated with the knowledge of correct use of Alu as direct observed therapy and its subsequent intake at home. Although not quantified, most of the caregivers who responded correctly to most of the questions related to malaria symptoms and use of Alu to treat uncomplicated malaria in underfives admitted to have heard through media broadcasts and routine health education given in the health care facilities. This could be the fruits to the efforts made by the MOHSW/NMCP in broadcasting through the media as well as routine health education given in the health facilities about malaria symptoms in children, appropriate actions and correct medication.

The positive relationship between socioeconomic status and knowledge of malaria symptoms and appropriate medication to use could be explained by the fact that among the indicators used in the assessment of socioeconomic status, was the possession of assets like radio and television in the household. If possession of these assets were linked to the acquisition of the knowledge, then we can explain the relationship of socioeconomic status and the knowledge examined. Contribution of health facilities' routine health education, radio and television broadcasts in the knowledge of malaria and its prevention has been studied in Tanzania<sup>88, 89</sup>. Although radio and television broadcasting messages are consistent and have potentially high frequency of exposure, they do not reach all target audiences because of the community affordability<sup>89</sup>.



Other factors examined like age and sex of the caregiver, his/her education level and religious affiliation were not associated with the knowledge of malaria symptoms nor with the knowledge of use of Alu to treat uncomplicated malaria in children aged less than 5 years.

#### **6.4 Malaria infection among those who had laboratory confirmed diagnosis**

Overall prevalence of uncomplicated malaria in the studied children who presented with fever and/or other symptoms suggestive of malaria was 24.8%, which is just above population prevalence of 20.8% in the study area. This difference can be explained by the fact that, the prevalence was calculated for the sick children who came to the health facilities with fever and/or other symptoms suggestive of malaria.

It is worth noting that by using the criteria used to make clinical diagnosis of malaria in this study setting, 11.5% of the children who were clinically diagnosed to have no malaria, had malaria parasites in their blood (post-test probability of presence of disease in clinically negative malaria = 0.115). These were those children diagnosed to have other febrile conditions like acute respiratory tract infections, UTI and skin infections and treated with antibiotics. However some, 3 out of 70 (4.3%) were presumptively prescribed with Alu. This is a serious omission of such a potentially fatal disease bearing in mind that malaria is the number one cause of morbidity and mortality in children aged less than 5 years in Tanzania<sup>64</sup>. Insensitivity of clinical signs and symptoms in suspecting malaria in children has been documented in other studies<sup>90</sup> and also the tendency for healthcare providers to adopt new methods and guidelines slowly<sup>80</sup>. This calls for more rigorous diagnostic criteria as well as adherence to the treatment guidelines by the healthcare providers, as these point out some other common symptoms of malaria in children besides fever such diarrhoea and vomiting, pallor, body weakness and loss of appetite. Continual relying on fever and anaemia as main predictors of malaria in children could introduce serious omission of true cases of potentially fatal disease like malaria who might present with symptoms other than fever.

However with likelihood ratio positive  $LR^+ > 1$  and  $LR^- < 1$ , presumptive diagnosis of malaria can still be used in settings where malaria transmission is intense throughout the year and where logistic and technical factors inhibit routine use of more sensitive and specific diagnostic facilities like microscopy and RDTs.

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 and management of febrile illness<sup>91</sup>.

On the other hand, post-test probability of absence of disease in clinically positive malaria was 0.74, that is clinical diagnosis criteria rules in large numbers of false positives. With large numbers of false positives, misdiagnosis of the disease and mistreatment with antimalarials, irrational use of expensive drugs like Alu and chances for development of drug resistance are imminent. A positive clinical malaria diagnosis is in itself poor at diagnosing true case of malaria (PPV = 26%) and so further investigations such as RDTs and microscopy must be undertaken where possible. Minimization of prescriptions (both antimalarials and antimicrobials) following use of microscopy and/ or other sensitive and specific diagnostic facilities has been demonstrated in other studies<sup>52</sup>. Clinical diagnosis alone has very low specificity and in many areas 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<sup>91</sup>.

### **6.5 Child's age, infection and quality of care and antimalarial prescription**

The infection and the parasite count above 1000 trophozoites/200 WBC were found to increase with age after the infancy. Several studies in Africa have demonstrated similar findings in that in areas of high malaria transmission, infection, parasite count and clinical manifestations of malaria in children were mild in the first year of life but increased markedly



thereafter from 12 to 60 months of age<sup>92</sup>. Maternal antibodies<sup>92</sup>, foetal haemoglobin<sup>93</sup> and HbAS<sup>94, 95</sup> have been implicated as explanations for these findings.

In this study, there were no significant differences between the age of the child and quality of case management and antimalarial prescriptions. This implies that infants who might not had malaria parasites were equally treated for malaria as were the children aged 1 to 5 years. Some important considerations have to be taken in efforts to develop more rigorous clinical criteria and their adoption to the guidelines. These should include not only seasonal and geographical variations in malaria transmission but also age variations in malaria infection, parasite count and clinical manifestations among children aged less than 5 years. Use of diagnostic clinical criteria which rules in large number of false positives in areas of low malaria transmission or during seasons of low malaria transmission may lead to overestimation of the cases. This applies as well to situations where there are age variations in the prevalence of disease. The consequence of overestimation of cases is the mistreatment with antimalarials, imminent development of resistance and mismanagement of other febrile illnesses. However, it has been observed in clinical practice that, currently there are malaria infection and malaria disease manifestations in infants as in 1-5 year olds in heavy malaria infection in endemic areas. This calls for research to find out the truth about this and possible reasons.



## CHAPTER 7

### 7.0 CONCLUSIONS AND RECOMMENDATIONS

#### 7.1 Conclusions

The study has demonstrated the need for promotion of an inter-disciplinary approach to achieving prompt and effective malaria case management in children aged less than 5 years in settings where diagnostic facilities are lacking. Prompt and effective malaria case management calls into action, not only individual patients, caregivers and health care providers but also the families, health care system and the community as whole. These comprise health care training system, economic and media systems and political system.

Prompt and effective malaria case management and prescription of recommended antimalarials is directly linked to early care seeking by the individuals within 24 hours of onset of symptoms, health care provider with appropriate training, enough consultation time by the health care provider so as to be able to take careful history and detailed examination of the patients and health care system which ensures the availability of recommended antimalarials in the health care facilities.

Accessibility to mass media messages which is linked to socio economic status and routine health education provided in the health facilities positively improve knowledge of caregivers on malaria symptoms in children as well as knowledge on the correct use of artemether-lumefantrine. The appropriate knowledge is in turn associated with early care seeking and consequently with appropriate malaria case management.

With likelihood ratio positive  $LR^+ > 1$  and  $LR^- < 1$  presumptive diagnosis of malaria can still be used in settings where malaria transmission is intense throughout the year and where logistic and technical factors inhibit routine use of more sensitive and specific diagnostic facilities.

However, there is a need for more rigorous clinical criteria, adherence to the guidelines by the

health care providers as these outline some other common symptoms of malaria in children besides fever for example diarrhoea and vomiting, pallor, body weakness and loss of appetite. Continual using of fever alone as main clinical predictor of malaria in children could introduce serious omission of true cases of potentially fatal disease like malaria who might present with symptoms other than fever.

On the other hand, post-test probability of absence of disease in clinically positive malaria shows that clinical diagnosis criteria rules in large numbers of false positives. With large numbers of false positives, overdiagnosis of the disease, overprescription of antimalarials, irrational use of expensive drugs like Alu and chances for development of drug resistance are imminent. A positive clinical malaria diagnosis is in itself poor at diagnosing true case of malaria (PPV = 26%) and so scaling up deployment such as RDTs and microscopy must be undertaken where possible.

## **7.2 Recommendations**

1. Individuals to frequently update their knowledge on symptoms, appropriate treatment of malaria and correct use of Alu by giving due attention to the health education they get through media and routine health education in the health facilities.
2. Health care providers to use at least 5 minutes with patients and caregivers in consultation as this have been shown to improve the quality of care. Spending at least 5 minutes in the consultation provides an ample time to carefully take history, adequately assess the illness and give rational medications. The effective use of work tools at hand like thermometers and routine measuring of axillary temperature in all children presenting to the facilities have been shown to discover febrile illnesses which were not spontaneously reported by the caregivers.
3. Health care providers should as much as possible adhere to diagnosis and treatment guidelines as these contain updated information on symptoms and recommended

drugs. When they are aware of range of symptoms, they can make appropriate diagnoses with minimal omissions.

4. The MoHSW/NMCP to continue mass media broadcasts as this has been observed to translate to good knowledge of malaria symptoms, early care seeking and knowledge on correct use of Alu.
5. The MoHSW/NMCP should scale up deployment of RDTs and microscopy facilities where possible.
6. Economic empowerment of rural population and women in particular. Improved socioeconomic status affords individuals and families with accessibility to health and information which in turn improve their knowledge and early health care seeking.
7. The plan to bring primary health care services for example dispensaries and home based care as close to the people in the rural areas as possible, should go hand in hand with the provision of appropriate human, technical and material resources for instance clinical officers, nurses, laboratory technicians, thermometers, RDTs, microscopy and sustainable supply of recommended antimalarials.



## REFERENCES

1. World Health Organization, World Malaria Report 2005. Geneva, WHO/HTM/MAL/2005.1102; 2005
2. Snow RW. Estimating mortality, morbidity and disability due to malaria among Africa's non-pregnant population. *Bulletin of the World Health Organization*, 1999, 77(8):624-40.
3. Ministry of Health Government of Tanzania. National Malaria Control Program; National Malaria Medium Term Strategic Plan, 2003–2007. Dar es Salaam, Tanzania: Ministry of Health. 2003.
4. Derriennic, Y, Katherine W. Costing Artemisinin-based Combination Therapy for Malaria in Tanzania. Bethesda, 2005
5. East African network for monitoring antimalarial therapy, The efficacy of antimalarial monotherapies, sulphadoxine-pyrimethamine and amodiaquine in East Africa, implication for regional policy; *Tropical Medicine and International Health*, 2003, 8:60-7
6. World Health Organization, World Malaria Report 2008. Geneva, WHO/HTM/GMP/2008.1; 2008
7. Trape JF. Impact of chloroquine resistance on malaria mortality. *Reports of the Academy of Sciences*, 1998, 321:689-697.
8. Greenberg AF. Hospital based surveillance of malaria related paediatric morbidity and mortality in Kinshasa, Zaire. *Bulletin of the World Health Organization*, 1989, 67(2):189-196.
9. Bloland PB, Ettlign M. Making malaria treatment policy in the face of drug resistance. *Annals of Tropical Medicine and Parasitology*, 1999, 93(1):5-23.

10. Price RN, Nosten F, Luxemburger C, ter Kuile FO, Paiphun L, Chongsuphajaisiddhi T, White NJ. Effects of artemisinin derivatives on malaria transmissibility. *Lancet*, 1996, 347:1654-1658.
11. World Health Organization, The use of antimalarial drugs. Report of a WHO Informal Consultation. Geneva, (WHO/CDS/RBM/2001.33, 2001
12. World Health Organization, Antimalarial drug combination therapy: Report of WHO technical consultation, Geneva, (WHO/CDS/RBM/2001.35; 2001
- 13.
14. Foster SDF. The distribution and use of antimalarial drugs - not a pretty picture. In: Targett GAT, ed. *Malaria: waiting for the vaccine*. Chichester, John Wiley & Sons Ltd., 1991:123-128
15. White NJ. Averting a malaria disaster. *Lancet* 1999;353:1965–1967.
16. Omari AA, Gamble C, Garner P. Artemether-lumefantrine (six-dose regimen) for treating uncomplicated falciparum malaria. *Cochrane Database of Systematic Reviews* 2005, Issue 4. Article. No: CD00556463.
17. White N. Antimalarial drug resistance and combination chemotherapy. *Philosophical Transactions of the Royal Society of London*, 1999, B(354):739-749.
18. White NJ. Preventing antimalarial drug resistance through combinations. *Drug Resistance Updates*, 1998, 1:3-9.
19. World Health Organization, The use of artemisinin and its derivatives as antimalarial drugs: report of a joint CTD/DMP/TDR informal consultation. Geneva, unpublished document WHO/MAL/98.1086, 1998.

20. Kamugisha ML. The effect of endemicity on the sensitivity and specificity of malaria case definition and attributable fraction in north-east Tanzania. *Tanzania Health Research Bulletin*, 2005, 7: 1–6
21. Wang S, Lengeler C, Mtasiwa D, Mshana T, Manane L, Maro G, Tanner M. Rapid urban malaria appraisal: Epidemiology of Urban Malaria in Dar es Salaam, Tanzania, *Malaria Journal*, 2006, 5: 28.
22. Makani J, Matuja W, Liyombo E, Snow RW, Marsh K, Warrell DA. Admission diagnosis of cerebral malaria in adults in an endemic area of Tanzania: implications and clinical description. *Quarterly Journal of Medicine*, 2003, 96: 355–362.
23. Reyburn H, Mbatia R, Drakely C, Carneiro I, Mwakasungula E, Mwerinde O, Saganda K, Shao J, Kitua A, Olomi R, Greenwood BM, Whitty CJ. Overdiagnosis of malaria in patients with severe febrile illness in Tanzania: a prospective study. *British Medical Journal*, 2004, 329: 1212.
24. James A Berkley, Kathryn Maitland, Isaiah Mwangi, Caroline Ngetsu, Brett S Lowe, Charles RJC Newton, Kevin Marsh, J Anthony G Scott, Mike English, Use of clinical syndromes to target antibiotic prescribing in seriously ill children in malaria endemic area: observational study, *British Medical Journal* 2005;330:995
25. Mboera LEG, Fanelo CI, Malima RC, Talbert A, Fogliati P, Bobbio F, Molteni F. Comparison of Paracheck-Pf test with microscopy for confirmation of *Plasmodium falciparum* malaria in Tanzania. *Annals of Tropical Medicine and Parasitology*, 2006, 100:115–122.
26. Dejan Zurovac, Mickey Ndhlovu, Alexander K Rowe, Davidson H Hamer, Donald M Thea, and Robert W Snow, Treatment of paediatric malaria during a period of drug



transition to artemether-lumefantrine in Zambia: cross sectional study, *British Medical Journal* 2005; 331: 734

27. Yeneneh H, Gyorkos TW, Joseph L, Pickering J, Tedla S. Antimalarial drug utilisation by women in Ethiopia: Knowledge-attitudes-practice study. *Bulletin of the World Health Organisation*, 1993, 71,763-77
28. Slutsker L, Chitsulo L, Macheso A, Steketee RW. Treatment of malaria fever episodes among children in Malawi: results of a KAP survey. *Tropical Medicine and Parasitology*, 1994, 45, 61-64.
29. Jayawardene R. Illness perception: social cost and coping-strategies of malaria cases. *Social Science and Medicine*, 1993, 37, 1169-1176
30. Mburu FM, Spencer HC, Kaseje DC. Changes in sources of treatment occurring after inception of a community-based malaria control programme in Saradidi, Kenya. *Annals of Tropical Medicine and Parasitology*, 1987, 81, Suppl-10.
31. Djimde A. Use of antimalarial drugs in Mali: policy versus reality. *American Journal of Tropical Medicine and Hygiene*, 1998, 59, 376-379.
32. Peters W. The prevention of antimalarial drug resistance. *Pharmacology and therapeutics*, 1990, 47: 497-508.
33. Masseur AY, Sayi J, Nsimba SE, Ofori-Adjei D, Laing RO. Knowledge and management of malaria in Dar es Salaam, Tanzania. *East African Medical Journal*, 1993, 70, 639-642

34. Gessler MC. Traditional healers in Tanzania: the treatment of malaria with plant remedies. *Journal of Ethnopharmacology*. 1995, 48, 131-144.
35. Mwenesi H, Harpham T, Snow RW. Child malaria treatment practices among mothers in Kenya. *Social Science and Medicine*, 1995, 40, 1271-1277.
36. Mwenesi H. (1994) Mothers' definition and treatment of childhood malaria on the Kenyan Coast. *Social and Economic Research Progress Reports*, 1994, 13, 48.
37. Foster S. Pricing, distribution, and use of antimalarial drugs. *Bulletin of the World Health Organization*, 1991, 69, 349-363.
38. Glik DC, Ward WB, Gordon A, Haba F. Malaria treatment practices among mothers in Guinea. *Journal of Health and Social Behaviour*. 1989 ;30(4):421-35.
39. Don de Savigny, Charles Mayombana, Eleuther Mwageni, Honorati Masanja, Abdulatif Minha, Yahya Mkilind, Conrad Mbuya, Harun Kasale. Care-seeking patterns for fatal malaria in Tanzania. *Malaria Journal* 2004, 3:27, 3-27
40. McCombie SC. Treatment seeking for malaria - a review of recent research, *Social Science and Medicine*, 1996, 43:933-945
41. McCombie SC: Self-treatment for malaria: the evidence and methodological issues. *Health Policy and Planning* 2002, 17:333-344.
42. Nuwaha F. People's perception of malaria in Mbarara, Uganda. *Tropical Medicine and International Health* 2002, 7:462-470.

43. Nyamongo IK. Health care switching behaviour of malaria patients in a Kenyan rural community. *Social Science and Medicine*, 2002, **54**:377-386
44. Warsame M, Kimbute O, Machinda Z, Ruddy P, Melkisedick M. (2007) Recognition, Perceptions and Treatment Practices for Severe Malaria in Rural Tanzania: Implications for Accessing Rectal Artesunate as a Pre-Referral. *PLoS*, 2007, 2(1):1371
45. H. Kristian Heggenhougen, Veronica Hackethal, Pramila Vivek. The behavioural and social aspects of malaria and its control. *Tropical Diseases Research/Social, Economic and Behavioral Research* vol 03, 2003.
46. Winch PJ. Local terminology for febrile illnesses in Bagamoyo District, Tanzania, and its impact on the design of a community-based malaria control programme. *Social Science & Medicine*, 1996, 42, 1057-1067
47. Schellenberg JRM, Victora CG, Mushi A, de Savigny D, Schellenberg D, Mshinda H, Bryce J. Inequities among the very poor: health care for children in rural southern Tanzania. *Lancet* 2003, 361:561-566
48. Muturi J, Haaland A, Watkins WM, Otieno G, Marsh K. Changing home treatment of childhood fevers by training shop keepers in rural Kenya. *Tropical Medicine and International Health* 1999, **4**:383-389.
49. Brugha R, Chandramohan D, Zwi A. Viewpoint: Management of malaria - working with the private sector. *Tropical Medicine and International Health* 1999, **4**:402-406
50. Oberlander L, Elverdan B. Malaria in the United Republic of Tanzania: cultural considerations and health-seeking behaviour. *Bulletin of World Health Organization* 2000, 78:1352-1357.



51. Mtango FDE, Neuvians D, Broome CV, Hightower A, Pio A. Risk factors for deaths in children under 5 years old in Bagamoyo District, Tanzania, *Tropical Medicine and Parasitology* 1992, 43:229-233
52. Olivar M, Develoux M, Chegou Abari A, Loutan L. Presumptive diagnosis of malaria results in a significant risk of mistreatment of children in urban Sahel. *Transactions of the Royal Society of Tropical Medicine & Hygiene* 1991;85:729-730.
53. Billy Ngasala, Marycelina Mubi, Marian Warsame, Max G Petzold, Zul Premji and Anders Bjorkman; 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; *Malaria Journal* 2008, 7:199
54. Redd SC. Usefulness of clinical case-definitions in guiding therapy for African children with malaria or pneumonia. *Lancet* 1992;340:1140-1143.
55. Smith T . Attributable fraction estimates and case definitions for malaria in endemic areas. *Statistics in Medicine* 1994;13:2345-2358.
56. Ronn AM, Msangeni HA, Mhina J, Wernsdorfer WH, Bygbjerg IC. High level of resistance of Plasmodium falciparum to sulfadoxine- pyrimethamine in children in Tanzania. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1996, 90(2):179-181.
57. Boele van Hensbroek M. Iron but not folic acid, combined with effective antimalarial therapy promotes haematological recovery in African children after acute falciparum malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1995, 89:672-676

58. East African network for monitoring antimalarial therapy, The efficacy of antimalarial monotherapies, sulphadoxine-pyrimethamine and amodiaquine in East Africa, implication for regional policy; *Tropical Medicine and International Health*, 2003, 8:60-7
59. McIntosh HM, Olliaro P. Artemisinin derivatives for treating uncomplicated malaria. *Cochrane Database System Review*, 2000.
60. Bunnag D Bunnag D, Karbwang J, Chitamas S, Harinasuta T. Intramuscular artemether in female patients with uncomplicated falciparum malaria. *Southeast Asian Journal of Tropical Medicine and Public Health*, 1993, 24(1):49-52.
61. Hien TT. An overview of the clinical use of artemisinin and its derivatives in the treatment of falciparum malaria in Viet Nam. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1994, 88(Suppl. 1):S7-S8.
62. von Seidlein L, Bojang K, Jones P, Jaffar S, Pinder M, Obaro S, Doherty T, Haywood M, Snounou G, Gemperli B, Gathmann I, Royce C, McAdam K, Greenwood B. A randomized controlled trial of artemether/benflumetol, a new antimalarial and pyrimethamine/sulfadoxine in the treatment of uncomplicated falciparum malaria in African children. *American Journal of Tropical Medicine and Hygiene*, 1998, 58: 638-644.
63. Vugt MV, Wilairatana P, Gemperli B, Gathmann I, Phaipun L, Brockman A, Luxemburger C, White NJ, Nosten F, Looareesuwan S. Efficacy of six doses of artemether-lumefantrine (benflumetol) in multidrug-resistant Plasmodium falciparum malaria. *American Journal of Tropical Medicine and Hygiene* 60: 936-942

64. White NJ, van Vugt M, Ezzet F. Clinical pharmacokinetics and pharmacodynamics and pharmacodynamics of artemether-lumefantrine. *Clinical Pharmacokinetics*, 1999, 37: 105–125
65. Tanzania Ministry of Health, National Malaria Control Programme, National Guidelines for malaria diagnosis and treatment. , Malaria control series 11, Dar es Salaam; National Malaria Control Program, 2006.
66. Gyapong JO, Agyepong I, Evans DB. Improving adherence to malaria treatment for children: the use of prepacked chloroquine tablets vs. chloroquine syrup. *Tropical Medicine and International Health* 2001, 6:496-504.
67. Gyapong JO, Asare IK, Barnish G, Evans DB, Adjei S. Impact of prepackaging antimalarial drugs on cost to patients and compliance with treatment. *Bulletin World Health Organization* 2001, 79:394-399.
68. Georgiev GD, Kielstrup RW. Blister calendar packs - potential improvement in the supply and utilisation of multiple drug therapy in leprosy control programmes. *International Journal of Leprosy*, 1988, 56(4):603-610.
69. Revankar CR, Dhamale CB, Ganapati R. Experience of multidrug therapy blister-calendar packs in an urban leprosy control programme in Bombay . *Leprosy Review*, 1991, 62(3):336-342.
70. Shwe T, Lwin M, Aung S. Influence of blister packaging on the efficacy of artesunate and quinine + tetracycline treatment of uncomplicated malaria in Thailand. *Bulletin of the World Health Organization*, 1998, 76:59-66.
71. WHO/TDR. The advantages of pre-packaged antimalarials. *Tropical Medicine and International Health* 1997, volume 8, 133–139



72. Cullinan TR, Pieterick C. Packaged treatment for first line care in cerebral malaria and meningitis. Geneva, World Health Organization, 1997, (unpublished document WHO/MAL/97.1083).
73. Agtmael M, Bouchaud O, Malvy D, Delmont J, Danis M, Barette S, Gras C, Bernard J, Touze JE, Gathmann I, Mull R. The comparative efficacy and tolerability of artemether + lumefantrine versus halofantrine in the treatment of uncomplicated falciparum malaria in travellers returning from the tropics to The Netherlands and France. *International Journal of Antimicrobial Agents* , 1999, 12: 159–169
74. Lefevre G, Looareesuwan S, Treeprasertsuk S, Krudsood S, Sila-chamroon U, Gathmann I, Mull R, Bakshi R. A clinical and pharmacokinetic trial of six doses of artemether-lumefantrine for multidrug-resistant Plasmodium falciparum malaria in Thailand. *American Journal of Tropical Medicine and Hygiene*, 2001, 64: 247–256
75. Jewett M, Miller N, Mzava N. Malaria Expenditure Analysis: Tanzania Case Study. Tanzania Household Budget Survey, Dar es Salaam, Government of Tanzania 1–54, 2000
76. Bloland BB, Ettling M, Meek S. Combination therapy for malaria in Africa: hype or hope? 2000, *Bulletin of World Health Organization*, 78: 1378–1388.
77. Cullinan TR, Pieterick C. Packaged treatment for first line care in cerebral malaria and meningitis. Geneva, World Health Organization, 1997 (unpublished document WHO/MAL/97.1083).
78. Gelband H, Sciter A. A global subsidy for antimalarial drugs. *American Journal of Tropical Medicine and Hygiene*, 2007, 77 : 219–221

79. Tarimo DS, Lwihula GK, Minjas JN, Bygbjerb IC. Mothers' perceptions and knowledge on childhood malaria in the holoendemic Kibaha district, Tanzania: Implications of malaria control and the IMCI strategy, *Tropical Medicine and International Health*, 2000, 5(3):179-84
80. National Bureau of Statistics, Tanzania National Projections based on 2002 Census. Mainland and Chief Government Statistician – Zanzibar , 2006.
81. Dejan Zurovac, James K Tibenderana, Joan Nankabirwa, James Ssekitooleko, Julius N Njogu, Malaria case-management under artemether-lumefantrine treatment policy in Uganda, *Malaria Journal* 2008, 7:181
82. Alexander K Rowe, Gabriel F Ponce de León, Quality of malaria case management at outpatient health facilities in Angola, *Malaria Journal* 2009, 8:275
83. Wasunna B, Zurovac D, Goodman CA, Snow RW: Why don't health workers prescribe ACT? A qualitative study of factors affecting the prescription of artemether-lumefantrine. *Malaria Journal* 2008, 7:29.
84. Rowe AK, Onikpo F, Lama M, Deming MS: Risk and protective factors for two types of error in the treatment of children with fever at outpatient health facilities in Benin. *International Journal Epidemiology* 2003, 32:296-303.
85. SA Lewin, J Dick, P Pond, M Zwarenstein, G Aja, B van Wyk, X Bosch-Capblanch and M Patrick, Lay health workers in primary and community health care: Cochrane systematic review; *International Journal of Epidemiology* 2005;34:1250–1253
86. Alinafe I Chibwana, Don P Mathanga, Jobiba Chinkhumba and Carl H Campbell Jr. Socio-cultural predictors of health-seeking behaviour for febrile under-five children in Mwanza-Neno district, Malawi; *Malaria Journal* 2009, 8:219
87. Sam Tumwesigire and Sharon Watson; Health care seeking by families of children suspected to have malaria in Kabale Uganda; *African Health Sciences*. 2002 December; 2(3): 94–98
88. Beatrice Amuge, Fred Wabwire-Mangen, Chilunga Puta, o, Nathan Bakyaaita, Sarah Staedke, Moses Kanya, and Olico-Okui Health-seeking behavior for malaria among

- child and adult headed households in Rakai district, Uganda; *African Health Sciences*. 2004 August; 4(2): 119–124.
89. F. Edson and E.J. Kayombo' Knowledge on malaria transmission and its prevention among schoolchildren in Kyela district, South-western Tanzania; *Tanzania Health Research bulletin*, vol. 9, no. 3, 2007, pp. 207-210
  90. Leonard E.G. Mboera, Susan. F. Rumisha, Kesheni P. Senkoro, Benjamin K. Mayala, Elizabeth H. Shayo And Wn. Kisinza; Knowledge And Health Information Communication In Tanzania; *East African Journal Of Public Health*, Vol. 4, No. 1, April 2007, Pp. 33-39
  91. Mwangi TW, Mohammed M, Dayo H, Snow RW, Marsh K; Clinical algorithms for malaria diagnosis lack utility among people of different age groups. *Tropical Medicine and International Health*. 2005 Jun; 10(6):530-6.
  92. Roll Back Malaria Department. Guidelines for the treatment of malaria, World Health Organization, Geneva, WHO/HTM/MAL/2006.1108, 2006
  93. Kitua AY, Smith T, Alonso PL, Masanja H, Urassa H, Menendez C, Kimario J, Tanner M.; Plasmodium falciparum malaria in the first year of life in an area of intense and perennial transmission; *Tropical Medicine and International Health*. 1996 1(4):475-84.
  94. R. J. M. Wilson, G. Pasvol, and D. J. Weatherall; Invasion and growth of Plasmodium falciparum in different types of human erythrocyte; *Bulletin of World Health Organization*. 1977; 55(2-3): 179–185.
  95. Benno Kreuels, Stephan Ehrhardt, Christina Kreuzberg, Samuel Adjei, Robin Kobbe, Gerd D Burchard, Christa Ehmen, Matilda Ayim, Ohene Adjei and Jürgen May; Sickle cell trait (HbAS) and stunting in children below two years of age in an area of high malaria transmission; *Malaria Journal* 2009, 8:16



## APPENDICES

### Appendix 1

#### English Version of the Questionnaire

#### Childhood Malaria Case Management in Kisarawe And Kibaha Districts, Tanzania, 2009-2010

##### Care Giver Information Form

Serial number..... Date of interview.....

##### Identification

Health facility..... Health care provider.....

Care giver..... Child.....

Child's information from the caregiver

1. Date of birth of your child.....

2. Sex of the child

1. Male                      2. female

3. What are the symptoms of the disease on your child?

1). Fever                      i. yes ii. No ( )

2). Headache                      i. yes ii. no ( )

3). Cough                      i. yes ii. No ( )

4). Joint pains                      i. yes ii. no ( )

5). Body weakness                      i. yes ii. no ( )

6). Vomiting                      i. yes ii. no ( )

7). Body ache                      i. yes ii. no ( )

8). Crying on urination                      i. yes ii. no ( )

9). Poor appetite                      i. yes ii. no ( )

10). Pallor                      i. yes ii. no ( )

11). Enlarged spleen                      i. yes ii. no ( )

12). Sore throat                      i. yes ii. no ( )

13). Running nose                      i. yes ii. no ( )